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ANNALS OF
INTERNAL MEDICINE

VOLUME 14 MAY, 1941 NUMBER 11

FACTORS INFLUENCING THE FATALITY RATE OF PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFONAMIDE COMPOUNDS *

By HARRISON F. FLIPPIN, M.D., F.A.C.P., LEON SCHWARTZ, M.D., and JEFFERSON H. CLARK, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

THE introduction of sulfapyridine and sulfathiazole in the treatment of pneumococcic pneumonia constitutes the greatest advance in the control of this disease. Within the past three years numerous clinical reports have unquestionably established their therapeutic effectiveness, and the fatality rate of pneumococcic pneumonia has been markedly reduced with their use. Despite the proved value of this form of therapy, a certain percentage of pneumonia patients in whom these drugs are employed fail to recover. The purpose of this paper is to discuss the influence of several factors on the prognosis of this disease. This report is based on our experience with 800 adult pneumococcic pneumonia patients treated during the past two years with sulfapyridine or sulfathiazole. In this group of 800 patients there were 80 deaths (10 per cent mortality, table 1).

TABLE I

Results of Chemotherapy in 800 Typed Cases

Type	Total Series			Negative Blood Cultures		Positive Blood Cultures	
	Number of Cases	Incidence Per Cent	Mortality Per Cent	Number of Cases	Mortality Per Cent	Number of Cases	Mortality Per Cent
I	185	23.1	7.0	150	6.0	35	11.4
II	48	6.0	10.5	43	4.7	5	60.0
III	139	17.4	20.0	125	15.2	14	64.3
Others	428	53.5	8.0	386	4.7	42	38.1
Total	800		10.0	704	6.8	96	32.3

Age of Patient. As indicated in table 2, 54.2 per cent of our cases were 40 years of age or over. In the fatal series 83.7 per cent represented patients in this same age group. The mortality rate was 3.5 per cent for those patients 12 to 39 years of age, as compared to 15.4 per cent in the higher age group. This significant difference in mortality rates is largely a result of

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the higher incidence of associated diseases in the older patients. In no other disease does youth, with the exception of the first year of life, prove as great an asset as in recovery from pneumonia. The age of the patient probably represents the most important single factor in the prognosis of this disease.

TABLE II

Influence of Age on Mortality

Age Group Years	Incidence Per Cent				Mortality Per Cent	
	Total Series		Fatal Series			
12–19	10.5		1.3		1.2	
20–29	16.9	45.8	5.0	16.3	2.2	3.5
30–39	18.4		10.0		5.5	
40–49	22.3		23.7		10.6	
50–59	15.3	54.2	27.4	83.7	18.0	15.4
60–69	10.8		17.6		16.4	
70 and over	5.8		15.0		26.1	

Time of Treatment. (Table 3.) In our entire series 65.3 per cent of the patients received treatment during the first four days of the disease with a mortality rate of 5.6 per cent, which represented 36.2 per cent of the fatal cases. Patients treated after the fourth day of illness (34.7 per cent) had a mortality rate of 18.4 per cent and constituted 63.8 per cent of the fatal series. Despite the effectiveness of chemotherapy, the length of time that elapses between the onset of the disease and the beginning of treatment has a definite bearing on prognosis. This is particularly so in patients treated after the fourth day of their illness.

TABLE III

Influence of Time of Treatment on Mortality

Day of Disease Treatment Started	Incidence Per Cent				Mortality Per Cent	
	Total Series		Fatal Series			
1	4.5		2.5		5.5	
2	18.1	65.3	11.2	36.2	6.2	
3	24.6		15.0		6.3	5.6
4	18.1		7.5		4.1	
5	12.8		18.7		14.7	
6	9.5	34.7	5.0	63.8	5.3	
7	5.1		8.8		17.1	18.4
7+	7.3		31.3		43.1	

Type of Infection. As shown in table 1, the first three types of pneumococci responsible for the disease constitute 46.5 per cent of the cases. Not only are they the most prevalent, but they also give the highest mortality rate (12.2 per cent). This is a result of the high incidence (17.4 per cent) of Type III infections which resulted in a mortality rate of 20 per cent as compared to 7.0 and 10.5 per cent for Types I and II respectively. The high mortality rate in this sub-group is explainable on the high incidence of Type III infection in elderly and debilitated patients. From these data it is apparent that the type of pneumococcic pneumonia has a direct bearing on prognosis.

Bacteremia. The incidence of bacteremia in this group was 12 per cent (table 1), whereas in the fatal series, 40 per cent had positive blood stream

infections. The high fatality rate (32.3 per cent) for this group of bacteremic patients demonstrates the influence of this condition on the prognosis of pneumonia.

Complications. Complications of pneumonia developed in 48 (6.0 per cent, table 4) of our patients. In 35 (4.3 per cent) patients included in this sub-group, the complications were mild and none of the patients died. However, in the remaining 13 patients who developed severe complications, the mortality rate was 53.8 per cent. Although the incidence of serious complications is low (1.7 per cent), this factor has a definite bearing on the patient's chances of recovery.

TABLE IV

Influence of Complications on Mortality

Complications	Incidence Per Cent		Mortality Per Cent
	Total Series	Fatal Series	
Massive effusions	3.3	—	—
Empyema	1.3	5.0	40.0
Meningitis	0.3	2.5	100.0
Endocarditis	0.4	3.8	100.0
Otitis media	0.4	—	—
Metastatic abscess	0.1	—	—
Phlebitis	0.5	—	—
*Total	6.0	8.8	14.6

* Corrected for patients having more than one complication.

Associated Diseases. In this series of 800 patients, 264 (33 per cent, table 5) had other disease conditions in addition to pneumonia. The incidence of associated diseases was arrived at, in most instances, by selecting the outstanding condition present in each case. However, this was not always adhered to, as in seven patients suffering with acute alcoholism there

TABLE V

Influence of Associated Diseases on Mortality

Disease	Incidence Per Cent		Mortality Per Cent
	Total Series	Fatal Series	
Heart disease	11.3	35.0	31.1
Syphilis	7.3	8.8	12.1
Alcoholism	5.5	11.3	20.5
Asthma	2.0	1.3	6.3
Diabetes mellitus	3.0	3.8	12.5
Active pulmonary tuberculosis	0.8	2.5	33.3
Nephritis	3.5	5.0	14.3
Cerebral hemorrhage	0.4	3.8	100.0
Pregnancy	1.0	0.0	0.0
Carcinoma	0.2	1.3	100.0
*Total	33.0	70.8	20.1

* Corrected for patients in whom more than one associated disease has been listed.

was evidence of cardiac disease, and these were recorded in both sub-groups. Furthermore, in 58 patients the diagnosis of syphilis was based on positive serological findings alone, except in eight instances where there was evidence of cardiac involvement, and these were also recorded under heart disease. With the exception of these 15 patients (seven alcoholic, eight luetic) there

was no further duplication in our figures. Unsuspected diseases were found at necropsy in several patients. No doubt in other instances we failed to detect associated conditions, because in only 45 (56.2 per cent) of the fatal cases were postmortem studies performed. This same possibility exists for the non-fatal group. Heart disease not only represented the highest incidence of associated disease but also resulted in the highest fatality rate (31.1 per cent) with the exception of carcinoma, cerebral hemorrhage, and active pulmonary tuberculosis. In many of the cardiac patients the pulmonary infection was well under control and in several had entirely disappeared, but death occurred as a result of progressive cardiac decompensation or acute coronary occlusion. The relatively low incidence of alcoholism (5.5 per cent) in this report is a result of our hesitancy to make this diagnosis on history alone. However, those patients in whom this condition has been diagnosed represent cases of acute alcoholism. As indicated, the mortality rate (20.0 per cent) for this sub-group is twice that of the entire series (10.0 per cent). The presence of pregnancy in eight patients without a death is of interest, in view of the expected high fatality rate of this condition prior to sulfonamide therapy. From these data it is apparent that the presence of certain associated diseases has a significant bearing on the prognosis of pneumonia. No doubt many of these patients suffering with pre-existing conditions would still be alive if pneumonia had not developed. However, the mere presence of many of these diseases results in a high incidence of pulmonary infections, such as pneumonia.

Race and Sex. It has been claimed that the race and sex of patients suffering with pneumonia have an influence on prognosis. In our experience (table 6) these factors appear to be of little or no significance.

TABLE VI

Influence of Race and Sex on Mortality

Race	Sex	Incidence Per Cent		Mortality Per Cent	
		Total Series	Fatal Series		
White	Male	45.3	46.2	10.2	9.8
	Female	27.1	25.0	9.2	
Colored	Male	17.2	21.3	12.4	10.4
	Female	10.4	7.5	7.2	

Place of Treatment. All of the patients referred to in this report are hospital treated cases. However, a word should be said regarding the comparative fatality rates of patients cared for at home, and in those who are hospitalized for treatment. With the widespread distribution and use of the sulfonamide drugs, more patients are being treated at home. Those in whom drug therapy has apparently failed at home are often sent to a hospital, and these usually represent seriously ill pneumonia cases. It is, therefore, apparent that more patients will probably now recover from

pneumonia than previously, although the mortality rate for this disease in hospitals may become increasingly higher.

Drug Toxicity. Because of certain toxic effects associated with the administration of these drugs, their use in pneumonia is sometimes prevented. If it is impossible to employ chemotherapy because of one of these untoward toxic manifestations, the patient's chances of recovery are reduced unless type specific serum is available. Furthermore, if certain of these toxic effects are overlooked, and the use of the drug is continued, it may lead to a more serious condition than that caused by the infection. Although we have observed several patients in whom drug toxicity necessitated stopping chemotherapy, there were no deaths attributable to the drug. In several instances it was necessary to administer type specific serum after discontinuing the drug. With the continued use of these compounds in many types of infections it is possible that more individuals will develop drug sensitivities, and the problem of the toxic effects of chemotherapy may become more acute in the future.

Other Factors. The patient's geographic location, as well as the fact of his living in a rural or urban community, influences the incidence and probably the prognosis of pneumonia. This report deals entirely with patients living in the city of Philadelphia, where, until recently, the expected mortality from this disease was 25 to 35 per cent. Of considerable importance is the economic status of the patient. Certainly we should expect a higher fatality rate in those who are inadequately sheltered, have occupations that expose them to cold and dampness, have poorly balanced diets, and possess unsuspected or untreated diseases. Furthermore, in some, because of financial reasons, or of slow mental activity, the seeking of medical aid is deferred until the patient's condition becomes alarming. The majority of our patients are from a low income class, and many are dependent on aid from relief agencies. Over-indulgence in alcohol, as shown in table 5, decreases the patient's chances of recovery; and also, because of the habits associated with alcoholism, the incidence of the disease is increased.

Discussion

Whether the mortality rate of 10 per cent, as reported in this paper for hospital treated cases, will be further reduced is a matter for conjecture. There is little reason to believe that the future will influence the incidence of the more severe types of infecting organism, the incidence of bacteremia, the age of the patient, the number of associated diseases, or the occurrence of alcoholism (table 7). However, we may, through widespread lay education, influence the number of patients who are treated during the first four days of their illness. If this is achieved we may expect a reduction both in the incidence of serious complications and in mortality rate from pneumonia. On this hangs the most important single factor in the future control of this disease. No doubt further experience will result in a better understanding and more intelligent use of these drugs and serum in the

future and this may decrease the present fatality rate. However, the widespread distribution and administration of sulfonamide therapy in pneumonia will have a definite influence on hospital practice. More of our cases will be treated at home, and only the severe ones will be sent to a hospital.

TABLE VII

Summary of Significant Factors Influencing Mortality Rate

Factors		Incidence Per Cent: Total Series 800 Cases	Incidence Per Cent: Fatal Series 80 Cases	Mortality Per Cent 10.0%
Age	12–39	45.8	16.3	3.5
Years	over 39	54.2	83.7	15.4
Type of infection	I and II	29.1	22.5	7.7
	III	17.4	33.8	20.0
	Others	53.5	43.7	8.1
Bacteremia		12.0	40.0	32.3
Day of disease	1–4	65.3	36.2	5.6
Treatment started	over 4	34.7	63.8	18.4
Complications		6.0	8.8	14.6
Associated diseases		33.0	70.8	20.1

This will undoubtedly result in a reduction in the general mortality, but the fatality rates in hospital treated cases will not be reduced. In fact, it is our impression that in the future we may expect even higher mortality rates from hospitals than those that have been reported during the past several years.[1, 2, 3, 4, 5, 6]

SUMMARY

1. Eight hundred pneumococcic pneumonia patients are presented, in whom sulfonamide therapy was employed. There were 80 deaths.

2. The influence of certain factors on the prognosis of the disease is discussed.

3. The future with respect to the fatality rate of pneumonia is considered.

We wish to express our thanks to John J. Shaw, M.D., Secretary of Health, Commonwealth of Pennsylvania, for his interest and help in this and related studies on pneumonia.

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THREE CASES OF ACUTE SYPHILITIC NEPHROSIS IN ADULTS *

By E. White Patton, M.D., *Nashville, Tennessee,* and Marvin B. Corlette, M.D., *Pasadena, California*

Three patients with acute syphilis have been seen in this clinic during the past two years who exhibited the picture of nephrosis and whose course justified a diagnosis of acute syphilitic nephrosis. Since there are few reports of similar cases in the literature, one is led to conclude that this is a rare complication of early syphilis. In 1935 Hermann and Marr [1] reviewed the literature on clinical syphilitic nephropathies and devised a classification of these conditions. They found nine cases which were considered characteristic of acute syphilitic nephrosis. Since Hermann and Marr's contribution, there have been no other reported cases of typical acute syphilitic nephrosis in the literature available to us. Baker [2] recently published an excellent case study of a 25 year old male with evidence of secondary syphilis and a nephrotic renal syndrome. But in this case the clinical picture was confused by the presence of an enlarged heart which rapidly returned to normal size as the patient improved. Because of the circulatory abnormality it is impossible to regard this as an instance of acute syphilitic nephrosis. Of the reported cases less than half have come from the United States. Only one is from the southeastern United States where the incidence of syphilis is generally considered the highest in this country.

According to Hermann and Marr acute syphilitic nephrosis is characterized by an abrupt onset of the nephrotic syndrome in patients who are in the late primary or secondary stage of syphilis. Typical features include massive edema and albuminuria, low total blood serum proteins with particular depletion of the albumin fraction, oliguria, elevated blood cholesterol, lowered basal metabolic rate, a strongly positive complement fixation test for syphilis and, finally, prompt recovery following anti-syphilitic treatment. Frequently doubly refractile lipoid bodies are found in the urinary sediment. Significant elevation of the blood pressure, eye ground changes, impairment of renal function, hematuria and cylindruria are usually absent. These abnormalities characterize a syndrome which differs significantly from the other clinical types of syphilitic nephropathies, namely simple syphilitic albuminuria and subacute and chronic syphilitic nephrosis. However, the latter types seem closely related to the syndrome of acute syphilitic nephrosis and are distinguished from it principally by evidence of less renal and systemic involvement in the case of simple albuminuria and by the differences in time of onset, chronicity and response to specific therapy in the subacute and chronic nephrotic types.

* Received for publication December 7, 1940.
From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

The three cases from the Vanderbilt University Hospital satisfy most of the criteria proposed by Hermann and Marr for acute syphilitic nephrosis, and are reported below:

Case Reports

Case 1. J. S., a 57-year-old white man, developed an acute urethral discharge six weeks before admission to the Vanderbilt University Hospital. This was treated elsewhere without improvement and at the time of his first visit he exhibited a purulent urethral discharge and a generalized macular rash involving the palms and the soles. The blood Wassermann and Kahn tests were positive. The patient was given two injections of neoarsphenamine which were separated by an interval of three days and consisted of 0.6 gm. each. Twenty-four hours after the second injection he noted oliguria and edema of the ankles. The edema became progressively worse until the time of admission four days later.

The past history revealed several episodes of acute urethral infection, presumably gonorrhea, but nothing suggestive of nephritis. There was no history of previous syphilitic infection and the blood Wassermann and Kahn tests were said to have been negative five years before the present illness.

Physical Examination: The patient did not appear acutely ill. He exhibited a fading diffuse macular rash which involved the soles and palms. There was a general glandular enlargement. The eye-lids were not edematous and the ophthalmoscopic findings were normal. The peripheral vessels were not remarkable. The blood pressure was 136 mm. of Hg systolic and 80 diastolic. The heart and lungs were normal. No abdominal viscera were palpably enlarged. There was a purulent urethral discharge and a severe balanitis. The prostate was enlarged, tender and boggy. Both lower extremities were quite edematous. The reflexes were normal.

Laboratory Findings: The specific gravity of the urine was 1.030; albumin ("4 plus") was present and there were many hyaline and granular casts and occasional white and red blood cells in the centrifuged sediment. No doubly refractile bodies were observed in the urine. He excreted 75 per cent of phenolsulphonphthalein in a two hour period. The non-protein nitrogen of the blood was 26 mg. per 100 c.c.; cholesterol 333; total serum proteins 5.30 gm. per 100 c.c.; serum albumin 2.51; serum globulin 2.79. The Wassermann and Kahn tests on the blood were strongly positive. The red blood cell count was 4.3 million per cu. mm.; white blood cell count, 10,000; hemoglobin 12 grams per 100 c.c. The differential leukocyte count was normal. A stool examination revealed no blood or parasites. The basal metabolic rate was +4 per cent.

Course: A high protein, salt poor diet was prescribed and fluids were restricted to 2000 c.c. in 24 hours. He was confined to bed. On this regimen he continued to excrete in the urine approximately 15 gm. of albumin daily and no change occurred in the urinary sediment. Six days after admission he was given 0.1 gm. and three days later 0.2 gm. of neoarsphenamine. Three days after the second injection the amount of albumin in the urine fell abruptly to 2 grams in 24 hours. Subsequently the albuminuria rapidly disappeared. Within nine days after the first treatment with neoarsphenamine the total serum proteins had risen to 6.05 gm. per 100 c.c. of blood, the albumin to 3.33 and the globulin fraction was essentially unchanged.

The patient was discharged from the hospital free of symptoms. Anti-syphilitic treatment was continued in the out-patient Syphilis Clinic where he has been followed regularly for the past two years. During this period he has completed the prescribed courses of treatment. The Wassermann and Kahn tests on the blood have become negative and the cerebrospinal fluid is normal. The blood pressure has remained normal and at no time has he complained of urinary tract symptoms. Repeated ex-

aminations of the urine have revealed normal values for specific gravity, occasional faint traces of albumin, and rare white blood cells in the centrifuged sediment. No red blood cells or casts have been observed. The non-protein nitrogen, total serum proteins and albumin-globulin ratio of the blood have remained normal.

Case 2. L. M. B., a negress aged 22, was admitted to the hospital complaining of backache and edema about the eyes. Two weeks before admission she noted the onset of dull pain in the lumbar region. One week later mild dysuria and frequency occurred. This was followed in two days by the development of puffiness of the eyelids. She denied the occurrence of manifestations of early syphilis.

Her past history was essentially negative. She had always experienced excellent health and there was nothing in the history suggestive of a previous attack of acute nephritis. She had noted chronic vaginal discharge for five years. Four months before the present illness Wassermann and Kahn tests on the blood were negative. These examinations were made in the laboratories of this hospital.

Physical Examination: She exhibited moderate edema of her eyelids but otherwise appeared quite well. There were numerous pigmented scars over the face and back. There was no general glandular enlargement but one large, firm, discrete gland was present in the left inguinal region. The retinae were very pale but were normal otherwise. There were no mucous patches in her mouth. The lungs were not remarkable and the heart was normal except for a systolic murmur heard best at the pulmonic area. The retinal and peripheral vessels were not abnormal. The blood pressure was 130 mm. of Hg systolic and 76 diastolic. No abdominal viscera were palpable. On the left labium majorum there was a healed scar, slightly elevated, about 2 cm. in diameter. The pelvic examination revealed chronic endocervicitis with moderate purulent discharge. Minimal pretibial edema was present. The reflexes were normal.

Laboratory Findings: A catheterized specimen of urine contained a huge amount of albumin ("4 plus"). The specific gravity was 1.018 and the reaction acid. The urine contained numerous hyaline casts but no red blood cells or white blood cells. Doubly refractile bodies were not observed. A culture of the urine yielded no growth. Blood studies revealed a hypochromic microcytic anemia; red blood cell count, 4.49 million; white blood count, 7,800; hemoglobin 7.8 gm. per 100 c.c. of blood. The differential white blood cell count was normal. The Wassermann and Kahn tests on the blood were positive. The total serum protein of the blood was 5.72 gm. per 100 c.c.; albumin 2.44 and globulin 3.28. The non-protein nitrogen of the blood was 29 mg. per 100 c.c.; cholesterol, 250; blood chlorides, 577. The patient excreted 50 per cent of phenolsulphonphthalein in one hour. The basal metabolic rate was minus 2 and minus 12 on successive days. Cervical smears revealed intracellular gram negative diplococci. Darkfield examinations of fluid obtained from the inguinal lymph node and from the healed scar were positive for *Treponema pallida*. No spirochetes were observed in repeated darkfield examinations of the urine centrifugate. A specimen of urine centrifugate was injected into the testicle of a rabbit. The rabbit did not develop syphilis.

Course: Bed rest and a high protein, low salt diet were prescribed. Fluids were limited to 1400 c.c. in 24 hours. During the first three days the output of urine ranged between 700 and 1100 c.c. with persistent albuminuria ("four plus"). Spontaneous diuresis then occurred. The patient excreted from 2000 to 2600 c.c. of urine daily for four days. This was associated with a rapid decline in the amount of albumin, which after the fourth day entirely disappeared. The output of urine then diminished to approximately 1000 c.c. daily. The low total serum protein and the reversed albumin-globulin ratio persisted. Neoarsphenamine (0.3 gm.) was given on the twelfth hospital day. Four days later a second injection, 0.45, was administered. Nine days after instituting specific therapy the serum albumin rose to 4.10 while the globulin remained at 3.21 gm. per 100 c.c.

Throughout the period of hospital observation the patient's blood pressure, temperature, and pulse remained normal. Following the administration of iron, the hemoglobin rose rapidly to a normal level and the patient was discharged free of symptoms. Anti-syphilitic treatment was continued in the Out-Patient Department.

Twenty months after treatment was instituted the urine contained no albumin. The specific gravity of a single specimen was 1.026. The non-protein nitrogen of the blood was 31 mg. per 100 c.c.; the total serum proteins, 6.54 gm.; the albumin-globulin ratio normal. During the period of anti-syphilitic treatment she experienced no symptoms of kidney disease and her blood pressure remained normal. Under treatment the Wassermann and Kahn tests became negative and the cerebrospinal fluid proved to be entirely normal.

Case 3. A. M. M., a negress aged 19, considered herself perfectly well until three weeks before admission to this hospital. At this time she noted an enlarged non-tender inguinal lymph node. One week later she developed a generalized cutaneous rash and a non-tender swelling of her left labium majorum. During the ensuing two weeks she experienced gradually increasing discomfort on urination at the site of this labial lesion.

As a child she had several severe sore throats but never any symptoms suggesting nephritis. Otherwise she gave no history of any previous illness. During her only pregnancy, one year before the present illness, she experienced no frank toxic symptoms.

No history of a primary syphilitic lesion could be obtained.

Physical Examination: The patient appeared quite comfortable. There was definite swelling of the soft tissues about the eyes and slight pitting edema of the forehead. A maculopapular rash was distributed irregularly over the extremities and trunk. The lymph nodes were generally and discretely enlarged. The mucous membranes were slightly pale. No mucous patches were observed. The retinal and peripheral vessels appeared normal and no retinal hemorrhages or exudates were present. The blood pressure was 90 mm. Hg systolic and 50 diastolic. There was a faint systolic murmur at the pulmonic area but otherwise the heart and lungs were entirely normal. No abdominal viscera were palpably enlarged. The left labium was markedly swollen and slightly indurated. Both labia exhibited excoriated areas. There was slight pitting edema of the lower extremities. The reflexes were normal.

Laboratory Findings: On admission a catheterized urine specimen revealed albuminuria ("4 plus"), occasional white blood cells, no red blood cells and rare granular casts. No doubly refractile bodies were seen in the urine. She excreted 45 per cent of phenolsulphonphthalein in the first hour and 15 per cent in the second hour. On a Fishberg test regimen she attained a maximum urinary concentration of 1.032. The non-protein nitrogen of the blood was 21 mg. per 100 c.c.; cholesterol 151; icteric index 1.5; sodium chloride 561; total serum proteins 5.95 gm. per 100 c.c.; serum albumin 2.80; serum globulin 3.15. The Wassermann and Kahn tests on the blood were strongly positive. The red blood cell count was 4.73 million per cu. mm.; white blood cell count, 6000; hemoglobin, 9 grams per 100 c.c. The differential leukocyte count was normal. A roentgen-ray examination of the chest and an electrocardiogram revealed no abnormalities. A catheterized urine specimen was centrifuged promptly and the centrifugate examined by the darkfield method. No *Treponema pallida* were seen. The centrifugate was injected into a rabbit's testicle. No syphilitic lesion developed. Darkfield examinations of the serum from the vulval lesion were positive for *Treponema pallida.*

Course: The patient was given an unrestricted diet and the fluid intake was not limited. Heavy albuminuria persisted for two days after the initial examination, and then abruptly decreased to only a trace. Subsequently she was given a blood serum transfusion of 100 c.c. and a whole blood transfusion of 500 c.c. She was given an

uninterrupted fever treatment at which time her rectal temperature was maintained at 41.5° Centigrade for 15 hours. She bore this treatment well but the urine continued to contain a faint trace of albumin for three days. Two days after artificial hyperpyrexia the blood non-protein nitrogen was 23 mg. per 100 c.c. of blood but there was no increase in the serum albumin value over the admission determination. Five days after fever therapy *Treponema pallida* were found on darkfield examination of serum from the vulval lesion.

No arsenical therapy was given this patient for a period of four weeks after therapeutic hyperpyrexia. During this period albuminuria entirely disappeared. She then experienced a recurrence of syphilitic skin lesions. Albuminuria did not recur. At the time of the cutaneous relapse the blood non-protein nitrogen was 24 mg. per 100 c.c. and the total serum proteins were 6.00 gm. per 100 c.c. of blood with an albumin value of 4.20 gm. Treatment with arsphenamine was then instituted. She has received four doses, 0.3 gm. each, of arsphenamine without untoward reactions.

Discussion

The pathology of acute syphilitic nephrosis is quite obscure. Post-mortem studies have been made only on subjects who had been exposed during life to poisoning from arsphenamine or mercury. Warthin [3] described tubular changes in the kidneys in a case of secondary syphilis and albuminuria. However, arsphenamine poisoning was the cause of death and doubtless complicated the renal findings. Dieulafoy [4] described similar renal changes but in this instance mercury had been employed therapeutically.

In the absence of satisfactory pathological studies it has been postulated that the passage of spirochetes through the renal tubules may be the cause of the nephrosis. Vorpahl,[5] Hoffman,[6] and Fiessinger and Huber [7] have reported the presence of *Treponema pallida* in the urine of syphilitic patients. Warthin subsequently recorded the demonstration of spirochetes passing into the renal tubules of several subjects who had had acute syphilis. These reports have been subjected to much criticism both as regards the specific nature of the spirochetes and the accuracy of the clinical diagnoses.

No attempts to demonstrate the presence of spirochetes in the urine by animal inoculation have been reported previously. This was done in two of our cases. The centrifugates of urine obtained by catheterization were injected into the testicles of rabbits. No syphilitic lesions developed. The collection, centrifugation and injection of the specimens were carried out rapidly. The negative results in two typical cases of syphilitic nephrosis cast considerable doubt upon the hypothesis that the passage of spirochetes through the tubules is an important factor in the pathogenesis of acute syphilitic nephrosis.

Two injections of neoarsphenamine, separated by an interval of three days and consisting of 0.6 gm. each, were given to the first patient and the onset of nephrosis occurred one day after the second treatment. It seems extremely unlikely that arsenic caused the nephropathy since the latter disappeared while the patient was receiving additional treatment with neoarsphenamine. The rapidity with which the nephropathy disappeared

following the reinstitution of treatment was impressive. However, no treatment factor operated in cases 2 and 3, since the development of the nephropathy antedated the institution of specific therapy. Moreover, spontaneous remission of symptoms and signs without benefit of anti-syphilitic treatment occurred in these cases. This has not been recorded heretofore in acute syphilitic nephrosis. In the light of the observation that spontaneous remissions do occur it appears reasonable to assume that the nephrotic syndrome may develop and undergo spontaneous remission without recognition by either patient or physician.

Summary

1. Three cases of acute syphilitic nephrosis are reported.

2. In two cases unsuccessful efforts were made to demonstrate *Treponema pallida* by inoculating rabbits intratesticularly with urine centrifugates.

3. In two cases the nephrotic syndrome underwent spontaneous remission without benefit of antisyphilitic treatment.

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THE HORMONAL, CENTRAL AND RENAL ORIGIN OF "ESSENTIAL" HYPERTENSION (CEREBRAL AND RENAL ARTERIOSCLEROTIC ISCHEMIA AS CAUSAL FACTORS) *

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Experimental Facts

There exist several experimental methods of producing persistent arterial hypertension: (1) section of the cardio-aortic and carotid sinus "moderator nerves" [1-3]; (2) impairment of the cerebral blood flow through either intracranial injection of kaolin suspension [4] or ligation of most of the vessels which supply the brain circulation [5]; (3) impairment of the renal blood flow [6, 7]; (4) repeated intramuscular injections of "hypertonin," which is obtained through ultra-filtration of the serum of hypertensive patients,[8] and of various hormonal sterols.[165]

Elevation of blood pressure following section of the moderator nerves, although a phenomenon of outstanding theoretical interest, apparently has no bearing upon the problem of arterial hypertension in man, as there are neither anatomical [9, 145, 146] nor clinical [147, 148, 149] signs of an alteration of the moderator nerve system in clinical arterial hypertension.

Artificial Central Hypertension. Artificial impairment of the cerebral blood supply as produced through intracranial kaolin injections [4] or ligation of the brain vessels [5] causes local shortage of oxygen. Shortage of oxygen is followed by an accumulation of unoxidized lactic acid and other metabolites in the brain tissue,[141, 142, 143, 144] and lactic acid not only stimulates the cerebromedullary vasoconstrictor centers but also increases their reactivity to various other kinds of stimuli.[10, 24] Both the pressor effect of stimulation of peripheral nerves and of CO_2 inhalation and the depressant effect of loss of CO_2 through hyperventilation are intensified during perfusion of the brain stem with blood containing added amounts of lactic acid [10] (see table 1). Analogous conditions are usually found in clinical "essential" hypertension. The stimulating and sensitizing effect of cerebral ischemia upon the vasoconstrictor centers has been fully confirmed by Heymans [153] and Heymans, Nowak and Samaan.[154] Gellhorn and Lambert [166] also have recently repeated and confirmed the experiments of Raab [10] concerning the increased vasomotor irritability due to shortage of oxygen. However, the claim of these authors that this phenomenon is not of a central nature is incompatible with well established facts and evidently based upon the misleading effects of anesthesia in their experiments.

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Artificial Renal Hypertension. The mechanism of arterial hypertension during artificial impairment of the renal blood supply [6, 7, 25, 26] does not seem to be of a primarily nervous nature as it occurs also after denervation of the kidneys,[27] after sympathectomy,[28] after destruction of the spinal cord,[186] and even if the kidneys are entirely isolated and connected with the body only through cannulas.[29] However, its abolition by pithing [167] suggests some participation of the central vasomotor apparatus.

TABLE I

Experiments on Decerebrate Cats (Raab [10])

	No. of Experiments	Average Reaction of Systolic Blood Pressure in mm. Hg
CO_2 inhalation normal	7	+27
CO_2 inhalation during shortage of O_2	7	+46
CO_2 inhalation normal	9	+26
CO_2 inhalation during perfusion of brain stem with lactic acid	9	+48
CO_2 inhalation normal	6	+18
CO_2 inhalation after injection of lactic acid into sub-occipital cavity	6	+46
Hyperventilation normal	9	+ 7
Hyperventilation during perfusion of brain stem with lactic acid	9	−23
Faradisation of crural nerve normal	9	+24
Faradisation of crural nerve during perfusion of brain stem with lactic acid	9	+49

Opinions concerning the rôle of the suprarenal glands in experimental renal hypertension are contradictory. Some authors [25, 30] consider it as essential, others [31, 32, 33, 152] do not. Formation of vasopressor substances within the ischemic kidney tissue itself has been made probable by various authors.[34, 35, 36] Cortical hormones of the suprarenal glands are believed to intensify their effect.[162] Normal kidney tissue has been found to contain blood pressure lowering substances both with acute [176] and with slow and prolonged action.[177, 178, 179] According to recent investigations [180] the "hypertension mediator" substance seems to be destroyed by normal metabolic activity of the kidneys. Tyrosinase counteracts artificial renal hypertension.[188]

A participation of humoral (renal?) factors both in the centrogenous "kaolin hypertension" and in its abolition through denervation of the kidneys [37] is suggested by the effects of transfused blood of such experimental animals.[173]

Artificial Hormonal Hypertension. Westphal and Sievert [8] succeeded in producing prolonged elevations of blood pressure by injecting "hypertonin," a supposedly hormonal substance which they had isolated from the serum of hypertensive patients. It increases the size of the suprarenal glands and is

effective only in their presence. Its blood pressure-elevating effect is enhanced by cholesterol.

Vasopressin from the posterior pituitary lobe, if injected into the suboccipital cavity, raises the blood pressure for a few hours,[38, 39, 40] probably through cerebral vasoconstriction and local ischemia.[174] Anterior lobe preparations are ineffective.[40] The presence of the pituitary gland does not seem to be indispensable for the production of experimental renal hypertension,[32] although the latter is diminished after hypophysectomy.[41]

Various purified hormonal sterols, such as desoxycorticosterone, estradiol, progesterone and testosterone were found to produce hypertension in rats, supposedly due to "renal injury."[165] Also in human individuals hypertension was brought about by the administration of desoxycorticosterone acetate.[183]

Compounds of cortical lipoids and adrenalin exert an intensifying effect upon the development of experimental arteriosclerosis[23] (see figure 1) and

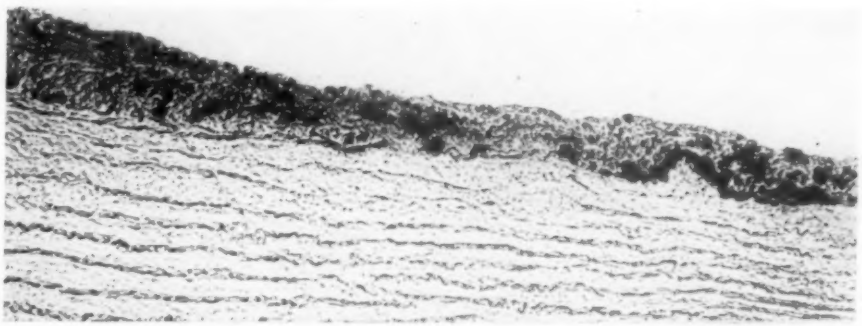

FIG. 1. Atheromatosis (cholesterol deposits) in the intima of rabbit's aorta after 35 days' preparatory treatment with suprarenal extract (288 mg. lipoid-adrenalin compound) and subsequent cholesterol feeding (7 gm. in 14 days). In untreated animals it takes at least two months' cholesterol feeding to produce this effect. (Raab.[23])

act as peripheral vasoconstrictors.[42, 43] Sterols of probably adreno-cortical origin have been found by the author to be present in the tissue of arterial walls.[182] Abnormally large amounts were observed in the arteries of a case of cortical adenoma. The degree of sensitization of the blood vessels to the vasoconstrictor effect of renin[162] may depend partly upon the composition and concentration of these hormones in their muscular tissue. Adrenalin itself can also be formed in the adrenergic neurons of the arteries[44] and its vasopressor effect is enhanced by the presence of cortical sterols (figure 2).[181, 187]

Vogt[43] observed an increase of vasopressor substances of supposedly suprarenal origin in the blood in centrogenous "kaolin hypertension."[4] However, the presence of the suprarenal glands is not indispensable for the production of this type of hypertension.[184, 185]

According to Steinach, Peczenik and Kun [45] the cerebral circulation decreases after castration but is restored to normal through the administration of sex hormones. The authors consider this phenomenon as important for both the pathogenesis and therapy of arterial hypertension.

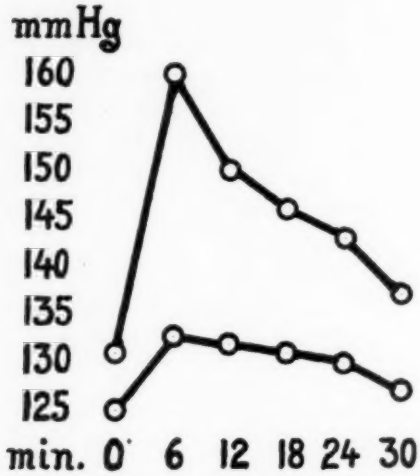

FIG. 2. Intensification of the blood pressure effect of adrenalin (0.5 mg.) through pretreatment with desoxycorticosterone acetate (Cortate Schering, 110–150 mg. within 4 to 6 days). Average of 6 experiments. Lower curve before, upper curve after administration of Cortate.

MORPHOLOGICAL FACTS

Central Changes. The existence of purely central forms of arterial hypertension in man has been demonstrated with certainty in those rather rare instances where hypertension developed suddenly with the onset of bulbar poliomyelitis [46, 47] or encephalitis,[149] after concussion of the brain [22, 48, 49] or after CO-poisoning,[50, 51] and where anatomical changes were found in the areas of the vasoconstrictor centers. However, these forms do not belong in the group of "essential" hypertension.

Arteriosclerotic changes which suggest the occurrence of local ischemia were found by Bordley and Baker [52] in the medulla oblongata of patients with essential hypertension. Cutler [53] and Tuthill [54] confirmed these findings in only about 50 per cent of their autopsied hypertensive cases, but Cutler emphasizes that, if present, they were always accompanied by arterial hypertension. Severe arteriosclerotic changes of the smallest vessels of the brain-stem of hypertensives have been described by Rühl,[55] and by Büchner and Wirtz.[56] The latter observed destructive changes of the brain-stem ganglia (of the same type as artificially produced through shortage of oxygen) in all cases of hypertension, even in young individuals. Trophic lesions of the brain-stem ganglia of the ischemic type have been found in essential hypertension also without visible anatomical changes of the brain vessels.[57, 58] They

are to be ascribed either to functional cerebrovascular spasms or to chemical alterations of the vascular walls which escape microscopic detection. This is the case, for instance, regarding small cholesterol deposits in the arterial walls which can be discovered only through chemical analysis [59] but may suffice to impair the gaseous exchange between blood and brain cells.[60] Plasma exudation around the small brain vessels, as is found in hypertensive cases, seems to have a similar detrimental effect upon the cerebral cellular oxygen supply.[61] Thus, shortage of oxygen within the cerebromedullary vasoconstrictor centers and its blood pressure elevating effect may be caused both by a diminution of vascular blood supply and by impairment of oxygen penetration into the cells of the centers.

An increasing lipoid infiltration and hyalinization of the smallest vessel walls and a gradual diminution of cerebral blood flow have been found to be common features of advancing age even in the absence of distinct atheromatosis of the larger brain vessels.[58, 62, 63, 64, 65, 66, 151] This fact is usually overlooked at routine autopsies. The brain tissue requires eight to ten times more oxygen than an equal volume of muscular tissue,[57] and even slight alterations of the cerebromedullary blood supply will probably not remain without functional consequences on the part of the vasomotor centers. It is true that cerebral sclerosis in general is not always accompanied by arterial hypertension. The occurrence or absence of the latter will depend upon the local distribution of vascular changes in those widespread areas of brain-stem and medulla oblongata where vasoconstrictor (and vasodilator?) centers are scattered, and also upon some factors of peripheral nature (condition of the heart, of the suprarenal glands, etc.). Gross arteriosclerotic changes of the brain were recorded in the necropsy findings of 87 per cent of 131 cases of arterial hypertension and in 41 per cent of 83 non-hypertensive mostly senile cases in some Vienna hospitals.[16] Statements concerning the much more important smaller cerebromedullary vessels were lacking throughout, as is usual in routine autopsy records.

Many authors have described cases of arterial hypertension with considerable arteriosclerosis of the brain but no vascular changes within the kidneys.[52, 67, 68, 69, 70, 71, 72, 150, 156] In cases like these the origin of the hypertension consists obviously in the stimulating and sensitizing effect of local ischemic asphyxia upon the vasoconstrictor cerebromedullary centers. It was Riebold's [67] merit to have established this fact in 1917 in a paper entitled "Permanent considerable arterial hypertension as an early symptom of cerebral arteriosclerosis."

Renal Changes. So-called "essential" hypertension, according to the original terminology, is characterized by the absence of clinically detectable signs of renal involvement, but there cannot be any doubt that in a great number of cases analogous vascular lesions to those in the brain are also, or even exclusively, present in the kidneys.[71, 73] Very often they do not manifest themselves clinically; nevertheless, their concealed presence may account

for marked elevation of blood pressure in accordance with the experimental findings of Hartwich,[6] Goldblatt,[25] Enger, Linder and Sarre,[26] etc. However, absence of high blood pressure has repeatedly been noted in spite of renal arteriolosclerosis.[74, 75, 76] The mode of production of vasopressor substances in the ischemic kidney is not yet clear, but there is some evidence that certain granulated cells in the walls of the juxtaglomerular portion of the afferent arterioles may be considered as their place of origin.[163, 164]

TABLE II

Arteriosclerosis and Gross Suprarenal Changes in Primary Hypophyseal Disturbances

Pituitary Disturbances	No. of Cases	Average Age Years	No. of Cases with Arteriosclerosis (% of Total No.)	Degree of Arteriosclerosis (% of Total No.)			Suprarenals (% of Total No.)*		
				−	+	++	Apparently normal	Enlarged	Atrophic
Anterior lobe basophilism and acromegaly	59	47	92	8	11	81	37	63	0
Adiposogenital dystrophy and hypophyseal cachexia	34	44	44	56	27	17	42	9	49

These figures were calculated from autopsy records which A. Ruggieri has collected in Vienna hospitals and from the literature. They give a rough impression of the relationship between pituitary hyper- and hypofunction with the condition of the suprarenal glands and the development of arteriosclerosis.

* The total number of findings concerning the suprarenals was 37 in the first and 27 in the second group.

The rather frequent complete absence of renal vascular changes in essential hypertension invalidates the view of some authors that renal ischemia is the sole cause of this disease. In addition to numerous other observations of permanent hypertension *without* vascular changes of the kidneys Fahr [156] has recently published 44 such cases which had been autopsied within a period of only two and a half years. Again in most of them macroscopically visible cerebral arteriosclerosis was recorded.

TABLE III

Reaction of Blood Pressure to Changes in the Alveolar CO_2 (Raab [16, 170])

	Type of Cases	No. of Experiments	Average Level of Blood Pressure mm. Hg	Average Reaction of Blood Pressure mm. Hg
Inhalation of CO_2	Acute glomerulonephritis	12	140	+ 6
	"Essential" and nephrosclerotic hypertension	40	178	+34
Hyperventilation	Normals	15	100	± 0
	Acute glomerulonephritis	6	163	± 0
	"Essential" and nephrosclerotic hypertension	40	198	−30

Changes of Endocrine Glands. The most outstanding anatomical changes of the endocrine system which are usually accompanied by arterial hypertension are basophile adenomata of the anterior pituitary and tumors of the suprarenal glands, both cortical and medullary.[23, 158, 159, 160, 161, 168] Also, non-tumorous increase of the basophile cells in the pituitary and mere hyperplasia of the suprarenals have been frequently observed in cases of hypertension.[23, 77, 78] Both features seem to be causally connected with each other through the "corticotropic" and "adrenotropic" activity of the pituitary anterior lobe. The latter may be increased even in those numerous cases of hypertension where no distinct morphological changes are found in the pituitary.[175]

The findings above mentioned apply not only to hypertension but also to arteriosclerosis in general which is intensely promoted through anterior pituitary and suprarenal activity [23, 79, 80] (table 2) even in infants.[157]

Clinical Facts

Central Hypertension. The following features indicate at least a participation of central nervous system pathogenic factors in the origin of "essential" hypertension:

(1) Fall of hypertensive blood pressure during sleep,[81, 82] during narcosis,[83] and during spinal anesthesia.[84, 85]

(2) Fall of hypertensive blood pressure during loss of CO_2 through hyperventilation,[11, 86, 87, 88, 89, 90, 91, 92, 93] a phenomenon which is completely or almost completely absent in normals [93, 94, 95, 96] and in purely "nephritic" hypertension (table 3, figures 3, 4, 5).[16, 90, 93] It corresponds to the experimental findings in animals whose brain stem has been artificially acidified.[10] Its origin is a central one and it is abolished in hyperventilation with gaseous mixtures containing sufficient CO_2 to maintain the alveolar CO_2 level unchanged (see figure 5).

(3) Fall of hypertensive blood pressure during diathermy of the skull [12, 97] in about 50 per cent of the cases, probably due to improvement of cerebral blood flow (table 4).

(4) Fall of hypertensive blood pressure after lumbar puncture.[68]

Table IV

Response of Blood Pressure Level to Diathermy of the Skull (Raab [12])

Type of Cases	No. of Cases	No. of Experiments	Average Blood Pressure Level mm. Hg	Average of Maximum Responses of Blood Pressure During Diathermy of the Skull. mm. Hg
Normals	12	12	113	+ 1
Reacting cases of "essential" and nephrosclerotic hypertension (about 50%)	15	47	192	−31

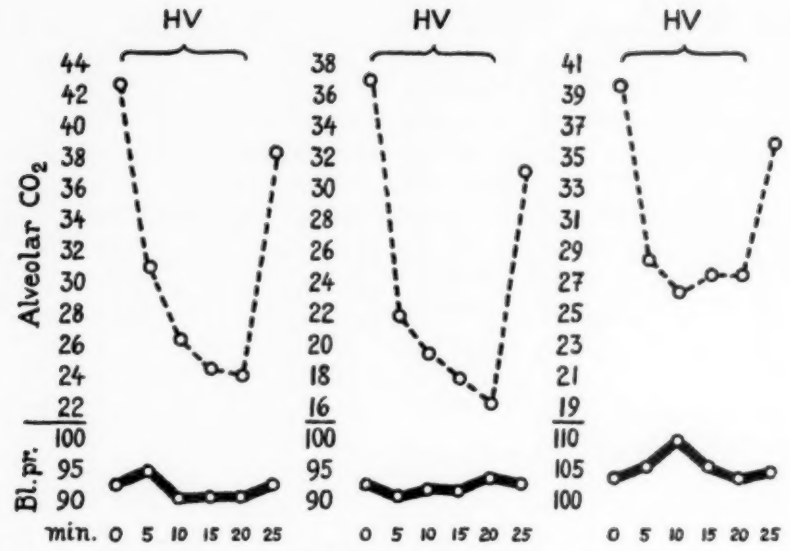

FIG. 3. Response of alveolar CO_2 and systolic blood pressure to hyperventilation (HV) in normals. (Raab.[11])

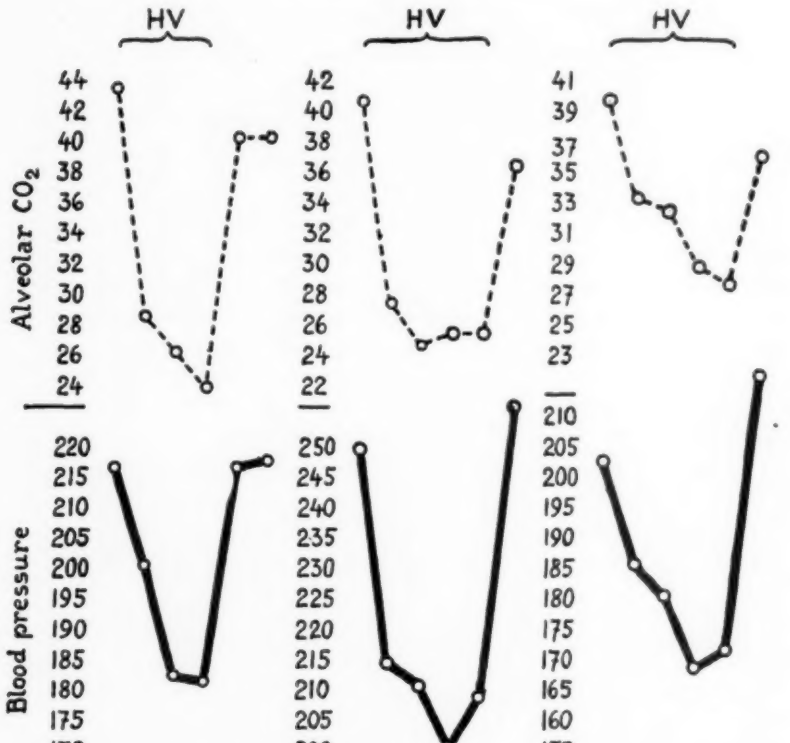

FIG. 4. Response of alveolar CO_2 and systolic blood pressure to hyperventilation in "essential" hypertension, indicating central vasomotor hyperirritability. (Raab.[11])

(5) The vasopressor response to inhalation of CO_2 is much greater in both hypertensive and non-hypertensive elderly persons than it is in young normals and in patients with nephritic hypertension.[19, 98, 99] Its abnormal increase corresponds to experimental findings in animals with anoxemia or direct acidification of the brain.[10, 24] It may be mentioned here that the

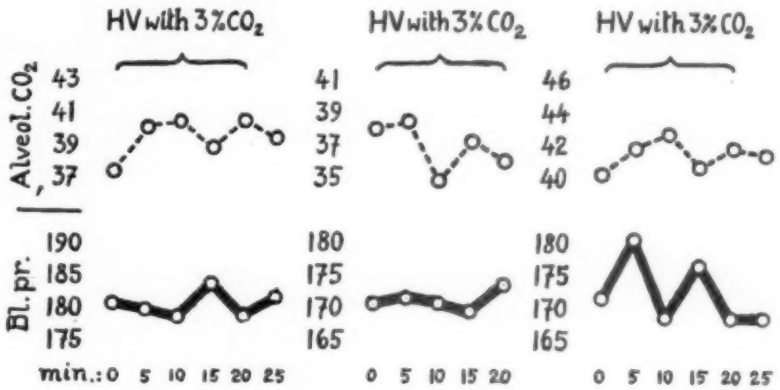

FIG. 5. Response of alveolar CO_2 and systolic blood pressure to hyperventilation with 3 per cent CO_2 in "essential" hypertension, demonstrating that prevention of loss of CO_2 also prevents the fall of blood pressure. This is evidence against the belief of some authors that the fall of blood pressure during hyperventilation is due to mechanical factors such as movements of the diaphragm, etc. (Raab.[11])

average response to quantitatively standardized CO_2 stimuli, as determined with a special technic, increases steadily with advancing age (figure 6).[13] This is probably due to the gradual decrease in blood and oxygen supply [58, 62, 63, 64, 65, 66] and to a corresponding increase in irritability of the cerebromedullary vasoconstrictor centers.

(6) Diminished vasopressor response of hypertensive patients to CO_2 inhalation following administration of padutin,[17] which exerts a distinct dilatory effect upon the brain vessels (table 5).[100, 101]

TABLE V

Response of Blood Pressure Level and of Central Reactivity to CO_2 under the Influence of Various Drugs in "Essential" and Nephrosclerotic Hypertension
(Raab and Friedmann[17])

Preparation Used	Dose	Duration of Experiments (Minutes)	No. of Experiments	Average Blood Pressure Level mm. Hg	Average Response	
					of bl. pr. level mm. Hg	to CO_2-test mm. Hg*
Morphine hydrochloride	0.02 gm. s.c.	60–105	3	165	− 6	−45
Luminal	0.1–0.2 gm. p.o.	60–120	12	162	± 0	−12
Padutin (Kallikrein)	24 units s.c.	20	13	173	+ 4	−18
Carbaminoylcholin-chloride (Doryl)	0.25 mg. s.c.	20–30	9	180	−23	+ 8

* The figures in this column indicate the difference in the degree of the blood pressure elevating effect of a standard CO_2 stimulus between the patients examined in this series and the average response of 25 persons of the same age groups.

(7) Increased vasopressor response to physical work,[16, 102] to holding the breath,[103, 104] to psychic emotion,[102] to pain,[105, 106] to cold,[107, 108] and to stimulation of the trigeminal nerve through the nose.[109, 110]

The increased blood pressure response to sensory stimuli corresponds to the reaction of animals with artificial acidification of the vasomotor centers.[10]

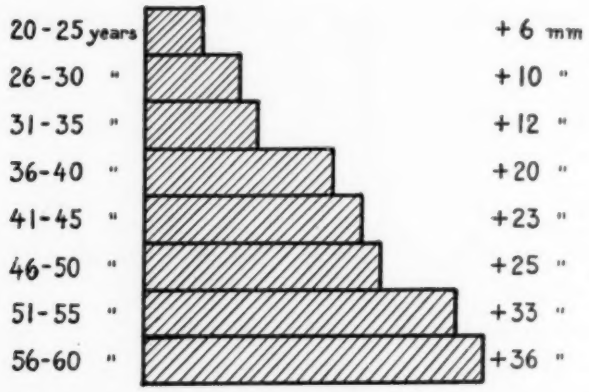

FIG. 6. Central vasomotor irritability increases with advancing age. The diagram shows the elevations of blood pressure due to a standard CO_2 stimulus (inhalation of CO_2 gradually increasing from 0 per cent to 7 per cent within 6 minutes) in 200 individuals with a normal blood pressure level. Every age group consists of 25 cases. (Raab.[13])

(8) The average oxygen utilization of the circulating brain blood is increased in hypertensive patients,[102] probably due to diminution of the cerebral circulatory volume (table 6).

TABLE VI

Cerebral Oxygen Utilization (Determined through Puncture of an Artery and of the Vena Jugularis Interna at the Base of the Skull) (Raab[14])

Type of Cases	No. of Cases	O_2-utilization in the Brain in % of the Arterial O_2 (average)	Investigators
Normals	10	35	Raab
	81	34*	Lennox
"Essential" and nephrosclerotic hypertension	10	43	Raab
	7	43*	Weiss and Ellis

* These figures were calculated from unpublished records which Dr. Wm. Lennox and Dr. Soma Weiss had been kind enough to lend me for comparison in 1930.

Some of the above mentioned phenomena are incompatible with the assumption of a purely renal pathogenesis of essential hypertension. They indicate, on the contrary, a participation of central factors in a large proportion of cases, thus corroborating a number of established experimental and morphological facts.

Renal Hypertension. It is unnecessary to discuss the symptoms which reveal to the clinician the presence of renal arteriolosclerosis. They are sufficiently well known, and as soon as any of them appear the term "essential" hypertension is no longer valid, as it refers to cases with no *clinical* signs of renal involvement.

Hormonal Hypertension. An increased anterior pituitary and suprarenal activity in "essential" hypertension as it is suggested by anatomical findings (see above) may also be deduced indirectly from certain clinical features, such as the common occurrence of hypertension in Cushing's syndrome and at the time of the menopause. An increased anterior lobe secretion is known to prevail in the aforementioned conditions and accordingly abnormally high amounts of prolan, of the corticotropic hormone of the anterior lobe, and of cortin have been found in the blood not only of these particular types of patients [109] but in essential hypertension in general.[111, 112, 113] The importance of anterior pituitary function for blood pressure regulation becomes evident from a statistical comparison of blood pressure levels in various primary hypophyseal disorders (table 7).

TABLE VII

Blood Pressure in Primary Hypophyseal Disturbances

Type of Hypophyseal Disturbance		No. of Cases	Average Age (Years)	Minimum Systol. Bl. Pr. (mm. Hg)	Maximum Systol. Bl. Pr. (mm. Hg)	Average Systol. Bl. Pr. (mm. Hg)	Normal Average Systol. Bl. Pr. at Corresponding Age (mm. Hg)
Hyperfunction of anterior lobe	Basophile Adenoma	25	29	95	300	189	120
	Acromegaly	24	45	104	270	142	140
Hypofunction of anterior lobe	Simmonds' disease	42	42	50	155	80	136
	Froehlich's disease and hypophyseal dwarfism	13	23	60	125	96	114

These figures were calculated from data collected by A. Ruggieri in Vienna hospitals and from the literature.—The "normal" blood pressure values were calculated from several statistical publications of the literature.

Whether the powerful vasopressor and corticotropic substance "hypertonin," which Westphal and Sievert [8] discovered in the serum ultrafiltrates of hypertensive patients, originates in the hypophysis is not yet decided. Hantschmann's work [114] seems to support this view. Other technical methods have failed to demonstrate the regular presence of abnormal amounts of hormonal vasopressor substances in the blood [115, 116, 117] and in the cerebrospinal fluid [118] of patients with permanent essential hypertension.

The manifold contradictions in the extensive literature on blood adrenalin in essential hypertension have been clarified in part by Konschegg.[42, 43] He comes to the conclusion that the vasoconstrictor effect of the usually normal amounts of adrenalin which are found in the blood of essential hypertensives is intensified through the formation of abnormally vasoactive compounds with cortical lipoids. In recent chemical investigations of the author, which will be published elsewhere,[170] there have been confirmed both the presence of normal adrenalin levels in the blood of essential hypertensives at rest and the formation of compounds of adrenalin with cortical sterols ("AC" compounds). Abnormally intense discharges of these AC compounds into the blood stream after bodily exercise were found in the majority of 25 cases of essential hypertension.[170] Also, during attacks of paroxysmal rise of blood pressure, which do not strictly belong in the group

TABLE VIII

Name	Age	Sex	Number of Series of Irrad.	Degree of Subjective Improvement	Duration of Improvement (Months)	Bl. Pr. Before Irrad. mm. Hg	Bl. Pr. at End of Observation mm. Hg
M. K.	47	♀	1	+++	24	230	270
M. H.	65	♀	2	+++	16½	220	196
D. T.	74	♂	1	+++	14	210	230
F. H.	72	♂	3	+++	12	210	220
J. S.	75	♂	3	+++	8	200	190
F. Z.	60	♂	1	++	3½	210	220
P. S.	53	♂	1	++	6	200	215
A. U.	61	♂	4	+	12	200	166
Average	63		2		12	210	213

Hypertensive patients with angina pectoris whose anginal attacks disappeared completely or partly after roentgen irradiation of the suprarenal glands while the blood pressure level remained practically unchanged. This speaks against a predominant rôle of suprarenal activity in the maintenance of stable essential hypertension (Raab[20]).

of "essential" hypertension, the adrenalin level of the blood has been found abnormally high.[117, 119] Roentgen-irradiation of the suprarenal glands is apt to prevent these attacks.[21] They are due either to a tumor or to a merely functional state of hyperactivity of the suprarenal glands. In ordinary essential hypertension, however, roentgen-irradiation of the adrenal glands, as a rule, does not depress the blood pressure level; not even in those numerous cases in which a reduction of adrenalin discharges during exercise, emotion, cold, etc., is evidenced by complete or almost complete and long-lasting relief of coexisting angina pectoris after roentgen treatment (table 8).[20]

Clinical Differentiation of Pathogenic Factors

Both cerebromedullary and renal arteriosclerotic ischemia can be present and can cause arterial hypertension despite the complete absence of the common clinical manifestations of cerebral and renal sclerosis.

Central Factors. Central vasomotor hyperirritability can be detected at normal or moderately elevated blood pressure levels through an increased vasopressor effect of measured CO_2 inhalation,[19, 98, 99] of holding the breath,[103, 104] etc. These methods are not reliable, however, at high blood pressure levels because the constrictive power of the vessel walls is limited. The hyperventilation test (drop of systolic pressure during 15 minutes of slow, deep respiration) gives somewhat clearer information. It is usually

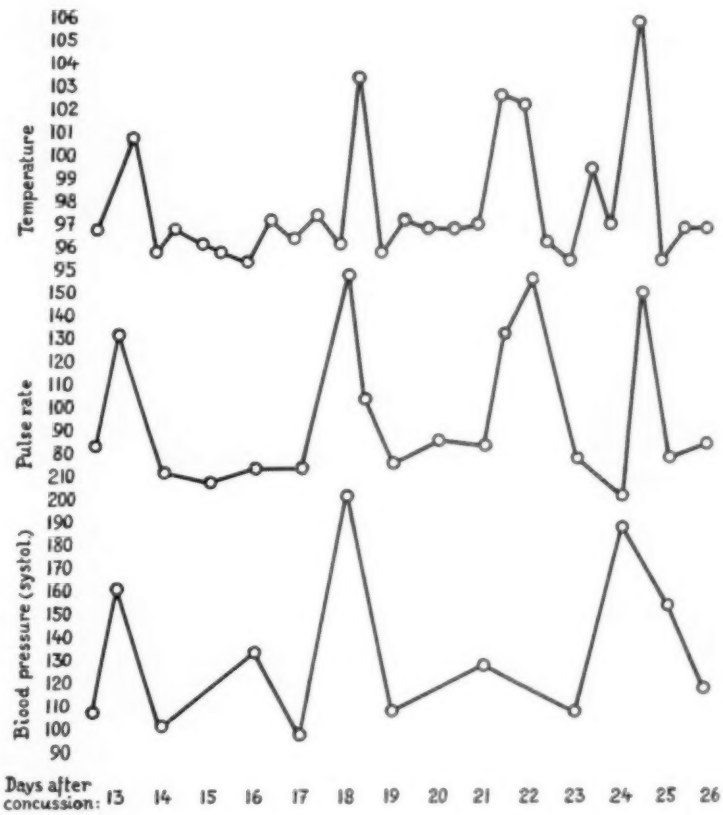

FIG. 7. Attacks of centrogenous arterial hypertension with fever and tachycardia after concussion of the brain in a 45 year old woman. (Raab.[22])

negative in normals,[93, 94, 95, 96] in purely nephritic hypertension,[16, 90, 93] and in a minority of cases of "essential" hypertension without clinical kidney symptoms.[16, 96, 121] It is usually positive in essential hypertension but sometimes also in "chronic nephritis."[121] Its significance consists exclusively in revealing the presence of a central hyperirritative pathogenic factor without indicating or excluding any other factors which may or may not be present at the same time. This is likewise true for other functional tests of central activity previously mentioned.

Arterial hypertension due to infectious, toxic or traumatic lesions of the vasomotor centers can be identified through the case history (poliomyelitis, encephalitis, CO-poisoning, concussion, etc.). The traumatic types of central hypertension appear sometimes in attacks which are associated with tachycardia and fever (figure 7).[22, 122]

Renal Factors. The appearance of clinical symptoms of arteriolosclerosis of the kidneys, such as albuminuria, hyposthenuria, etc., indicates directly the probable presence of a renal pathogenic factor in arterial hypertension. In these cases the hypertension is usually no longer called "essential" although the pathogenesis remains in principle the same. Before the

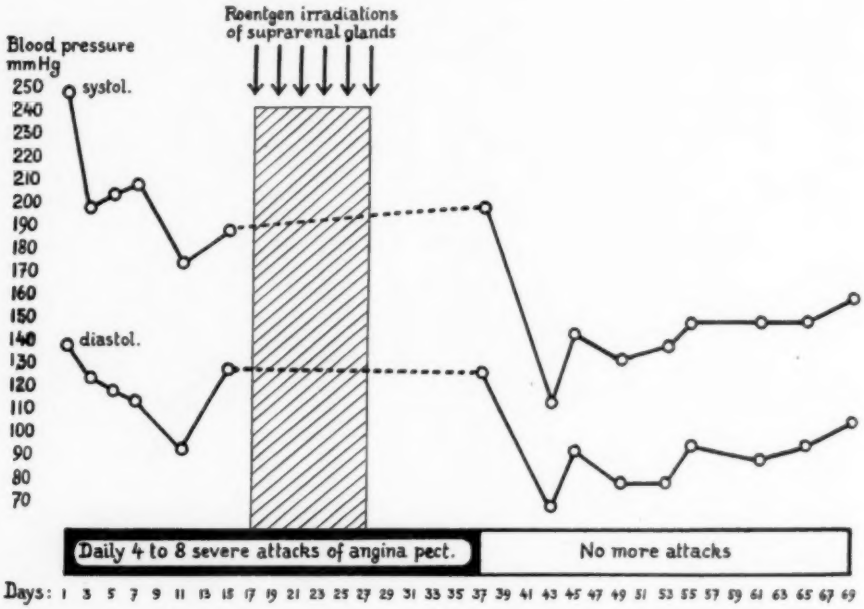

FIG. 8. Hypertension of apparently hormonal type in a woman aged 45 with severe attacks of angina pectoris relieved by roentgen irradiation of the suprarenal glands. The interval of about two weeks between treatment and clinical effect corresponds to the usual time of reaction to irradiation of the suprarenal glands.

onset of clinical kidney symptoms a prevailingly or exclusively renal origin of hypertension may be concluded indirectly from a negative hyperventilation test, high diastolic pressure, pale skin,[123] a history of pyelitis,[172] etc.

Hormonal Factors. The hormonal nature of hypertension is obvious in the presence of the typical features of Cushing's syndrome, such as purplish striae, obesity, "moon face," osteoporosis, hirsutism, etc. It is probable, if hypertension develops at the age of the menopause (figure 8) and in early diabetes. Tumors of the adrenal glands and paragangliomas with hormonal discharges may be diagnosed functionally from the acuity and characteristics of the attacks of hypertension (Pal's blood pressure crises[105]) and topically

from the pyelogram and the roentgen-ray picture after perirenal oxygen insufflation. A sudden intense rise of blood pressure immediately after massage of the adrenal region either on the right or left side may facilitate the localization of an adrenal tumor. A recently published modification of Shaw's method for the chemical assay of adrenalin in blood, which reveals the circulating amounts of adrenalin-cortical sterol ("AC") compounds,[171] yields normal values in plain essential hypertension but abnormally high ones in hypertension with renal insufficiency and in severe cardiac decompensation. In a two year old infant with periods of intense hypertension[170] abnormally high values were also found during the latter (figure 9).

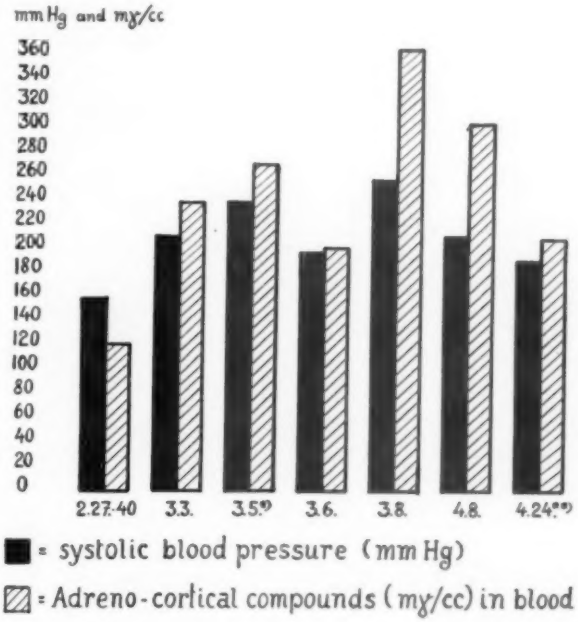

FIG. 9. Hypertension with slight renal involvement in a 2 year old child. In this case there was a closer parallelism of blood pressure and adreno-cortical compound level in the blood than in ordinary essential hypertension.

* After massage of right suprarenal region.

** In narcosis; 30 minutes after exposure of kidneys and suprarenal glands which showed no gross anomalies.

The stabilization of a previously labile blood pressure on a high level indicates the establishment of arteriolosclerotic vascular lesions in brain and kidneys, usually on a hormonal basis. The continuously repeated discharges of abnormally large amounts of suprarenal "AC" compounds into the blood stream, which are characteristic for "essentially" hypertensive individuals,[170] and the storage of these compounds in the vascular wall tissue[182] make the suprarenal glands appear to be the most important endocrine organs in this respect.

Prophylaxis and Therapy

Prophylactic measures against essential hypertension have to be directed primarily against anterior pituitary and suprarenal hyperactivity and against a constitutional predisposition to such hyperactivity. The following theoretical possibilities may be mentioned:

(1) Avoidance of generation by mates with a definitely arteriosclerotic and hypertensive pedigree;

(2) Lifelong avoidance of excessive amounts of foodstuffs which both stimulate the suprarenal glands and damage the vessel walls directly, namely cholesterol and ergosterol (vitamin D) in egg yolk, butter-fat and other animal fats;

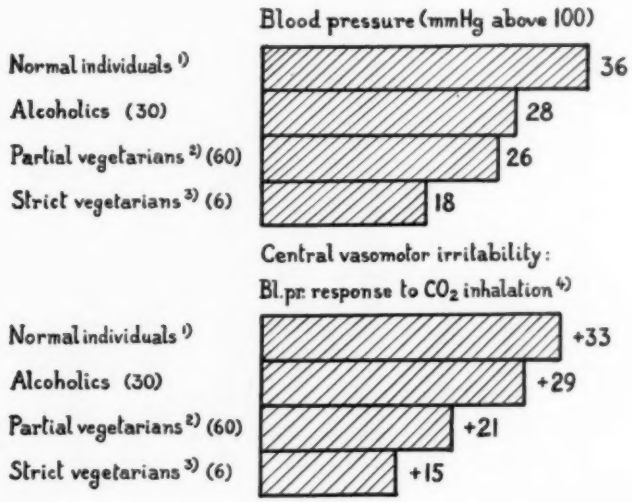

FIG. 10. The average age of each group was from 52 to 53 years.

1. The "normal" blood pressure level for the age of 53 years was calculated from several statistical publications of the literature.

2. Persons having refrained from meat but not from eggs and dairy products for an average period of 19 years.

3. Persons having refrained from all kinds of animal food including eggs and dairy products for an average period of 4 years.

4. The CO_2 standard stimulus was applied by inhalation of CO_2 gradually increasing from 0 per cent to 7 per cent within 6 minutes. An elevation of 33 mm. Hg is the normal average response of the blood pressure to this test at the age of 51 to 55 years. (Raab and Friedmann.[18])

International statistics, the results of a world wide inquiry by the author [15] and many experimental observations demonstrate the importance of the alimentary intake of large amounts of lipoids as a probable partial factor in the occurrence of arteriosclerosis and hypertension.[15, 124]

Some investigations which have been carried out in vegetarians show a lower average blood pressure level and a lesser central vasomotor irritability [125, 18] than in normally fed individuals of analogous age (figure 10);

(3) Avoidance of excessive tobacco smoking because of the adrenergic and arteriosclerosis-enhancing effect of nicotine [126];

(4) Avoidance of excessive mental strain because of its probable stimulating effect upon the suprarenal glands;

(5) Periodical roentgen-ray irradiation of the pituitary gland and the suprarenals in selected individuals who seem to be particularly endangered according to their pedigree or to an unusually early onset of clinical symptoms;

(6) Administration of sex hormones (chiefly female) in selected cases in due time to slow down climacteric anterior lobe and suprarenal hyperactivity.

Probably none of the measures mentioned above would in itself prove to be a definitely reliable means of protection against arteriosclerosis and hypertension but all of them appear theoretically well enough founded to be practically considered. Some of them have been used successfully in the treatment of hypertension, especially in its earliest stages, and in cases of a prevailingly hormonal vasoconstrictor type; for instance a diet free of eggs, milk, butter and milk-fat in juvenile hypertension [127] and in a number of adult patients [128, 129]; roentgen-ray irradiation of the pituitary and adrenal glands in some responding cases of essential hypertension [130] (see also figure 8), in paroxysmal hypertension [21] and in Cushing's disease [131, 132]; administration of sex hormones, particularly in climacteric hypertension.[45, 133]

There does not exist any satisfactory routine therapy for stabilized essential hypertension of the cerebral and renal arteriolosclerotic type. However, the blood pressure can be temporarily lowered through rest, hyperventilation, diathermy of the skull, sedatives, lumbar puncture, etc., not infrequently with prolonged relief of subjective complaints. The objective results of operative procedures, such as denervation of the suprarenals or the kidneys, are rather irregular and not always convincing.[134, 135, 136, 137, 138] In one case of malignant hypertension in a young man an excessively high level of adreno-cortical ("AC") compounds was found in the blood despite denervation of the adrenal glands.[170]

Encouraging attempts to counteract at least the renal factor in hypertension by the therapeutic administration of vasodepressant kidney extracts have recently been published by Page and co-workers.[178]

Summary

The establishment of our knowledge concerning the origin of "essential" hypertension has been greatly hampered for a long time through the endeavors of many investigators to demonstrate one or another single pathogenic factor as being solely responsible for the abnormal elevation of blood pressure. This has led to endless argument, contradiction and confusion. Today we know that various hypertensive mechanisms are, or at least may be, simultaneously present in the great majority of cases. Some of these

mechanisms can be demonstrated directly, as for instance central vasomotor hyperirritability; others may be inferred indirectly from animal experiments and from pathological postmortem findings, as for instance the formation of vasopressor substances in arteriolosclerotic kidneys. All pathogenic mechanisms of essential hypertension are originally connected with each other on the basis of a primary functional alteration of the endocrine system:

(1) Increased anterior pituitary activity stimulates suprarenal activity. This is the case in anterior lobe adenomata and both during and after the physiological involution of the gonads probably due to the decrease of their inhibiting influence upon the pituitary gland. Besides there exist also states of primary suprarenal hyperfunction (with or without tumors or hyperplasia of cortex and medulla and paragangliomas).

(2) The suprarenal glands not only produce cortical sterols and adrenalin separately but also compounds of both of these substances, which are apparently formed in the lacunae of the adrenal medulla and whose varying

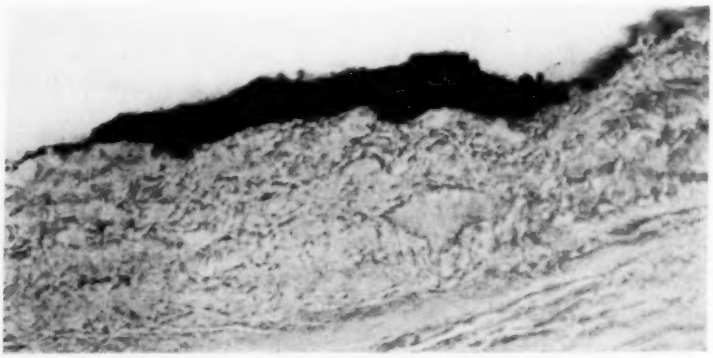

FIG. 11. Atheromatosis (cholesterol deposits) in the intima of rabbit's aorta after 43 days' preparatory treatment with extracts made from 1 liter serum of arteriosclerotic and hypertensive patients and after subsequent cholesterol-feeding (7 gm. in 14 days). In untreated animals it takes at least two months of cholesterol feeding to produce a similar effect. (Raab.[23])

composition seems to be of functional significance. They exert vasoconstrictor effects upon the blood vessels and, furthermore, they damage the arteries in the walls of which they accumulate through (*a*) degeneration of the media, and (*b*) marked acceleration of the deposition of alimentary lipoids (cholesterol, phosphatids) in the intima (see figures 1 and 11). In these ways they contribute to the development of arteriosclerosis.

(3) With the progress of arteriosclerotic changes of the small vessels both in the brain-stem, in the medulla oblongata and in the kidneys, two additional comparatively stable vasopressor mechanisms develop: (*a*) cerebromedullary arteriosclerotic ischemia causing an increased central vasoconstrictor tonus and increased central vasomotor irritability. It contributes to the raising of blood pressure to an abnormally high level and it causes

intensified vasopressor reactions to various stimuli. The objection that, in accepting this theory, one would have to expect simultaneous central dyspnea [123, 139] is based on a misconception, since the respiratory centers are much less sensitive to shortage of oxygen than the vasomotor centers [16, 140]; (*b*) renal arteriolosclerotic ischemia causes elevation of blood pressure through formation of vasopressor substances in the ischemic kidneys (renin which is later activated to angiotonin), possibly with sensitizing participation of a suprarenal hormonal factor.

(4) Every one of the three causally interrelated vasoconstrictor mechanisms, hormonal, central and renal, may appear alone, but usually all of them are present in the same case, although in a varying distribution. They can be clinically identified to a certain extent.

Conclusions

A survey of the international literature and of some original work leads to the following conclusions:

"Essential" hypertension can be caused by three pathogenic factors:

(1) Vasoconstriction due to hormonal effects upon peripheral vascular tonus (factor H). This mechanism is usually of only minor importance.
(2) Vasoconstriction due to increased central vasomotor tonus and irritability (factor C).
(3) Vasoconstriction due to formation of vasopressor substances in the kidneys (factor R).

The hormonal factor H is probably caused by a primary cortico-adrenotropic hyperactivity of the pituitary anterior lobe and a secondary, or also primary, hyperactivity of the suprarenal glands; the central factor C is caused by arteriolosclerotic ischemia and acidification of the cerebromedullary vasomotor centers; the renal factor R is caused by arteriolosclerotic ischemia of the kidney tissue.

There is a very close causal relationship between these three factors. Arteriosclerotic changes of the arteries are greatly enhanced by vasoactive compounds of cortical lipoids (sterols) and adrenalin. The suprarenal glands thus contribute directly to the factor H and indirectly to the factors C and R.

The pathogenic factors H, C and R can be present or partly absent in varying quantitative distributions. Renal changes are not infrequently completely lacking both macroscopically and microscopically.

For an approximate clinical characterization of the prevailing pathogenic mechanisms in individual cases of hypertension the terms "H type," "HR type," "CR type," etc., are suggested.

Prophylactic and therapeutic possibilities are briefly discussed.

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THE CLINICAL SIGNIFICANCE OF THE LOW OR "FLAT" ORAL GLUCOSE TOLERANCE CURVE*

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DURING the course of a study of sprue and allied deficiency states,[1] low or "flat" oral glucose tolerance curves were observed very frequently in the affected individuals. This was not a novel observation, for other observers had had the same experience, and furthermore, had suggested that this finding serve as a diagnostic aid in the recognition of sprue.[2, 3]

A review of the pertinent literature revealed considerable difference of opinion on the interpretation of the low oral glucose tolerance curve.[2, 4, 5, 6] It was felt that before relying too greatly upon the contour of the curve as a diagnostic aid in sprue, a satisfactory explanation of its cause was necessary.

With this point in mind, a series of 90 patients exhibiting "flat" or low oral glucose tolerance curves was studied. These patients constituted all of those with such curves seen in the Vanderbilt Clinic of the Presbyterian Hospital during the period of January 1933 to April 1939 inclusive. It was felt that a careful survey of this group might throw considerable light on the clinical significance of this type of blood sugar response as well as on the reason for its presence in sprue.

METHODS

In accord with the suggestion of Thaysen,[2] all curves showing less than 40 mg. per cent rise in blood sugar during the two to three hours following the oral administration of glucose were considered low. The dose of glucose was usually 100 gm. by mouth. In a few cases, the dose was 1 gm. per kilogram of body weight. The tests were done in the morning following an overnight fast. Specimens of venous blood and urine were obtained fasting and 30, 60, 120 and 180 minutes after glucose ingestion. The blood analyses were done according to the method of Folin.[7]

RESULTS

A total of 90 patients was observed. Their clinical diagnoses were as listed in table 1.

It is evident that the largest group of patients (28 cases or 31.1 per cent) with low oral glucose tolerance curves was that with dietary obesity. However, too great stress should not be placed on this high percentage, for,

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in this clinic, glucose tolerance tests have been done more often on patients with obesity than on those with any other disorder. It is not the purpose of this paper to report the number of obese subjects exhibiting this phenomenon. However, it can be stated that it is a frequent finding. The significance of this type of curve in obesity is under investigation [8] and will be made the subject of another report. Suffice it to say that there is little evidence to support the belief that it indicates lack of pituitary secretion in these cases. The explanation lies in the fact that these individuals are often huge consumers of carbohydrate—one confessing to eating, in addition to a liberal diet, one pound of sugar a day for three years! The ingestion of a high carbohydrate diet by normal individuals has been shown by Sweeney [9] and Himsworth [10] to result in flattened oral glucose tolerance curves or "increased tolerance" for carbohydrate. Himsworth [10] has studied this problem with much care and has advanced evidence for the belief that the flattening in the oral glucose tolerance curve caused by a high carbohydrate diet is produced by some factor which renders these patients highly sensitive to the effects of insulin. Regardless of the mechanism of its production, it remains established that a high carbohydrate diet alone in a normal individual may cause a flat or low oral glucose tolerance curve. In support of this thesis is the fact that when four of the obese subjects in the present study were placed on reducing diets, within a relatively short time their oral glucose tolerance curves returned toward normal.

TABLE I

Clinical States Associated with "Flat" Oral Glucose Tolerance Curves

Diagnosis	Number of Cases	Per cent of Total
Obesity—dietary	28	31.1
Renal glycosuria	11	12.2
Hypopituitarism	3	3.3
Hypothyroidism	9	10.0
Malnutrition and anorexia nervosa	10	11.1
Vitamin B complex deficiency	4	4.4
Hyperinsulinism	1	1.1
(??) Hypoglycemia	6	6.6
"Normal"	7	7.7
Hirsutism	4	4.4
Epilepsy	2	2.2
Migraine	2	2.2
Xanthomata	2	2.2
Pentosuria	1	1.1

The next group consists of 11 cases of renal glycosuria. We do not have quantitative studies of the urinary sugar output in these cases and therefore cannot say with certainty that renal elimination was the sole factor concerned in the production of these curves. It may be that accelerated glycogenesis occurs as a compensation for the renal loss of carbohydrate and contributes to the low curve. These findings emphasize the importance of analysis of urine secreted during the glucose tolerance test.

Group III consists of three patients with hypopituitarism. In these cases, the "flat" curve has been attributed to loss of pituitary secretion which ordinarily serves as an antagonist of insulin. Whether the mechanism is as simple as this is to be doubted in the light of recent experimental work [11] which indicates that in hypophysectomized dogs there is decreased absorption of glucose from the intestinal tract.

Group IV consists of nine patients with hypothyroidism. Here too the flatness of the curve has been ascribed to the lack of thyroid antagonism to insulin. However, recent experiments [12] have shown that in rats, thyroidectomy is followed by decreased absorption of glucose from the intestine.

Group V consists of patients with malnutrition. Patients similar to these have been said to have "chronic hypoglycemia." [13] This would appear to be a misnomer, for at no time do they have blood sugar below the normal range. They are underweight, have anorexia and often psychiatric difficulties. Whether their inability to respond to glucose ingestion with a rise in blood sugar constitutes relative hypoglycemia is a debatable point that will be discussed later. Those with more severe grades of this disorder have been labelled instances of anorexia nervosa. The cause for the low curve in these cases may be found in their dietaries, for these are often poor in fat and consist largely of carbohydrate. In addition to this, vitamin deficiencies are more frequent in these people than has been generally recognized. A deficiency in the vitamin B complex might well account for many of the symptoms and also contribute to the low curve.

Group VI consists of four cases which will be reported in more detail at a later date.[1] These patients present a clinical picture which is thought to represent deficiency of the vitamin B complex. Groen [14] has shown by direct measurements that intestinal absorption of glucose is definitely retarded in patients with deficiencies of the vitamin B complex. This is therefore a factor in the causation of the low oral glucose tolerance curve in this group.

One patient was found to have classical hyperinsulinism and was cured by the removal of an islet cell adenoma. In this connection it is of interest to note that a considerable number of patients (6 cases or 6.6 per cent) with low curves presented clinical symptoms suggestive of hyperinsulinism. Glucose tolerance tests were ordered in many instances with this diagnosis in mind. The presenting complaints of these patients were weakness, sweating, palpitation and nervousness, often relieved somewhat by food. Careful study did not support the view that they were suffering with pancreatic islet cell tumors. However, their inability to respond to glucose ingestion with a rise in blood sugar may account for some of their symptoms. On the other hand, most of the patients exhibiting this type of curve had no marked symptoms of hypoglycemia. Since the method used for determining blood sugar [7] measures other reducing substances in addition to glucose, it is possible that the patients with symptoms of hypoglycemia had more than the

usual amounts of non-glucose reducing substances in the blood. They would then have low true glucose values, possibly within the hypoglycemic range. Another possibility is that these patients, for some reason develop symptoms of hypoglycemia at higher levels than normal individuals. Obviously, this is a matter which merits further study.

The possible relationship between the low curve and hirsutism (4 cases), migraine (2 cases), epilepsy (2 cases) and xanthomata (2 cases) is not evident at present and the number of cases is too small to merit further comment.

A definite number of "normal" subjects (7 cases or 7.7 per cent) exhibit the low curve. However, in the absence of more complete dietary histories and other clinical details, too much stress cannot be laid upon the occurrence of this group. It is possible that some cause would be found on careful study.

In addition to the conditions enumerated above, a review of the literature indicates that low oral glucose tolerance curves are observed in sprue,[2, 3, 4] celiac disease,[2, 6] Addison's disease[16] and scleroderma.[15]

From these data, it appears that the low or "flat" oral glucose tolerance curve may be due to a number of known causes. These causes may, furthermore, be classified for the sake of clarity into three main groups:

A. Poor or slow absorption of glucose from the digestive tract
B. Rapid removal of glucose from the blood stream
C. Combinations of "A" and "B"

In table 2, the various clinical states associated with low oral glucose tolerance curves have been classified according to the above grouping. It is to be stressed that this classification is in many instances inadequate but it does have the attribute of simplicity and is presented merely as an aid in studying these cases. For obvious reasons no attempt has been made in this report to discuss the more fundamental mechanisms concerned in the disposal of ingested glucose. For instance, the rôles played by phosphorylation and diffusion in the absorption of glucose have not been defined, mainly because of the controversial nature of this subject at present writing.[5] As indicated in previous paragraphs, in the light of recent studies, there is room for dispute over the inclusion of certain endocrine disorders under the classification "B."

Sprue, the disorder which stimulated interest in the subject of this report, has been classified under "C" in table 2. To amplify this, it appears that in sprue, the low or "flat" oral glucose tolerance curve is caused by the following factors:

(1) The rate of absorption of glucose from the small intestine is definitely retarded. This has been established by the direct studies of Groen.[14] However, so far as the ultimate absorption of glucose is concerned, the hypomotility of the small intestine which also occurs in sprue may counter-

balance the slower rate and finally result in fairly complete absorption of glucose from the intestinal tract.

(2) The rate of removal of glucose from the blood stream in these cases is at least as rapid as normal and possibly slightly more rapid. This has been established by means of intravenous glucose tolerance curves.[1, 2]

(3) The diet of patients with sprue is often high in carbohydrate. Furthermore, because of the poor assimilation of fat, the diet that is actually absorbed is largely carbohydrate and protein. As has been indicated above, a high carbohydrate diet in a normal individual may cause a low oral glucose tolerance curve. This undoubtedly contributes to the "flat" curve seen in sprue.

TABLE II

Causes for the Low or "Flat" Oral Glucose Tolerance Curve

A. Poor or Slow Absorption of Glucose from the Digestive Tract
1. Edema, atrophy of mucosa and circulatory disturbances of the stomach and small intestine, e.g. sprue, vitamin B def., celiac disease
2. Inflammatory changes in the small intestine; tuberculosis, (?) ileitis
3. Neoplastic disease; tumors of the small intestine

B. Rapid Removal of Glucose from the Blood Stream
1. Mainly by accelerated glycogenesis and possibly in part by accelerated glucose combustion by means of .....
   (*a*) Excess of insulin or increased sensitivity to insulin —Hyperinsulinism. High carbohydrate diet
   (*b*) Lack of insulin antagonists
      (1) Lack of adrenal secretion—Addison's disease
      (2) Lack of pituitary secretion—Simmonds' disease. Hypopituitarism due to tumor or developmental defect. Hypophysectomy
      (3) Lack of thyroid secretion—Myxedema. Cretinism. Scleroderma (?)
2. Renal excretion ..... Renal glycosuria (phlorizin diabetes ?)

C. Combinations of "A" and "B"
Sprue
Malnutrition
Vitamin B complex deficiency states

When liver extract or other potent therapy is used in sprue, the glucose tolerance curve may become normal.[1] This is probably accomplished by restoration of the small intestine to normal so that all constituents of the diet are well absorbed. Failure to influence the glucose tolerance curve with liver extract may well be due to inability to restore normal function to the small intestine.

However, it must be stressed that if the diet of the sprue patient continues to be high in carbohydrate, the oral glucose tolerance curve may remain "flat" despite the restoration of the small intestine to normal.[1]

It is evident from the data presented above that many factors must be considered in interpreting the finding of a low or "flat" oral glucose tolerance curve. Most significant of all is the fact that a diet high in carbohydrate may by itself produce this type of curve. Therefore, before at-

taching diagnostic import to this response in any particular disease, the previous dietary regime of the patient exhibiting this phenomenon must be known. If this fact is kept in mind, many of the diverse and apparently unrelated clinical disorders exhibiting "flat" or low oral glucose tolerance curves may be seen to have one common denominator, the high carbohydrate diet. This does not imply that the type of diet alone is responsible for the contour of the oral glucose tolerance curve, for other forces are also concerned. However, in the present series of cases, in the absence of a disorder of the endocrine glands, the ingestion of a diet high in carbohydrate seems the most important cause for the "flat" oral glucose tolerance curve.

Summary

1. From a study of 90 patients exhibiting low or "flat" oral glucose tolerance curves, the causes for this type of curve have been defined.

2. A previous dietary regime high in carbohydrate is of great importance in causing the low or "flat" oral glucose tolerance curve.

3. This type of curve is not by itself diagnostic of any one disease, but may serve as a useful diagnostic aid.

4. The factors responsible for the low or "flat" oral glucose tolerance curve in sprue are discussed.

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THE CLINICAL SIGNIFICANCE OF THE BLOOD VOLUME *

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THE total quantity of circulating blood in normal humans and the nature and magnitude of the changes incident to disease have long been of interest to practitioners, but in the main these questions have remained a puzzle. Interest has waxed as new methods have been introduced and waned as they were found wanting. A review of methods extant is not intended. The dye injection method devised by Keith, Rowntree and Geraghty [1] in 1915 has been the most widely used of any, yet the numerous modifications of the original technic that have appeared [2, 3, 4, 5, 6, 7, 8, 9, 10, 11] indicate a feeling of doubt as to the reliability of the original method.

The results reported in this communication were obtained by the dye method developed by Gregersen, Gibson and Stead [12] as modified for clinical use by Gibson and Evans.[13a] This method accurately measures the plasma volume, total blood volume being calculated from plasma volume and hematocrit. It has proved to be reliable in this and many other clinics. A comparison of our findings with those obtained by earlier technics would contribute nothing to the purpose of this communication, which is to present certain facts about the blood volume in health and disease to the practitioner in the hope they may be helpful as a therapeutic background.

The Normal Blood Volume. The amount of circulating blood in the human body at rest varies with sex, body size and habitus.[13b] Males have a much larger total blood volume than females. In thin individuals absolute volume is lower and unit volume (in terms of height, weight or surface area) is higher than in well developed subjects of equivalent physical measurements, and the reverse situation obtains in obese individuals. In a group of 100 normal men and women of from 16 to 76 years of age the average range of total blood volume in relation to height and surface area was as shown in figure 1, the individual deviations from the curves shown being $\pm$ 15 per cent. Within these limits normal total blood volume for an individual may be predicted on the basis of physical measurements (figure 1). Assuming the normal hematocrit to be 44 for males and 40 for females, normal plasma and circulating red cell volume may be calculated from the total blood volume.

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In the studies reported herein, height has been used for the prediction of normal volume. In groups of patients with the same disease the average of the individual deviations from predicted normal volume is considered to be the change in blood volume characteristic of that disease.

Chronic Congestive Heart Failure. In chronic congestive heart failure total blood volume always is above normal,[13c] and the degree of elevation of volume is related to the severity of failure. Thus, average total blood volume in a group of patients with organic heart disease but with neither symptoms nor physical signs of failure was normal; in a group with symptoms but without physical signs of failure slightly above normal; in a group with mild congestive failure about 20 per cent above, and in a group with severe failure 55 per cent above normal. As failure progresses, the hematocrit tends to rise but is rarely over 50.

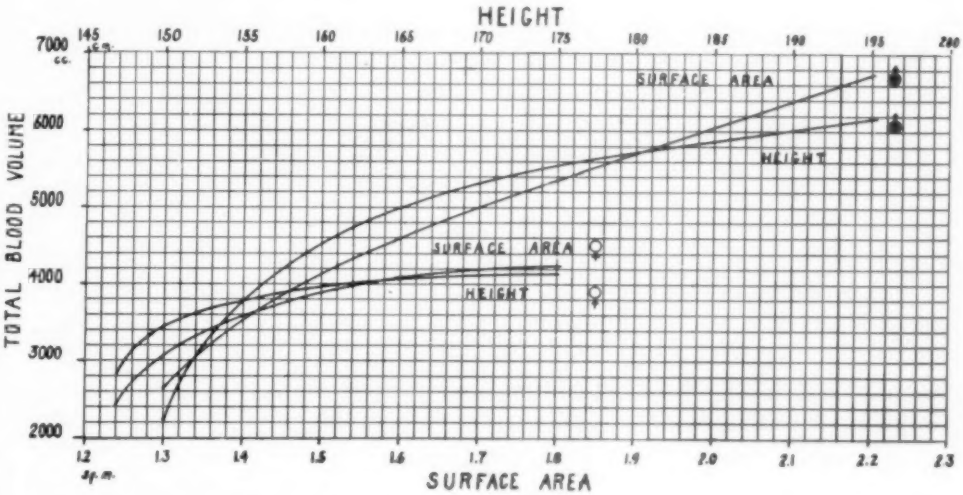

FIG. 1. Nomogram for predicting normal total blood volume in adult men and women. Plasma and circulating red cell volume may be calculated assuming the normal hematocrit to be 44 for males and 40 for females.

The course of the blood volume closely parallels the clinical conduct. Compensation invariably is accompanied by a decrease in total blood volume which may amount to from 500 c.c. to 1500 c.c. There is first a greater reduction in plasma than in circulating red cells so that the hematocrit may rise as the total volume falls. Later, with continued improvement, plasma volume decreases further but at a diminished rate, and the reduction in red cells becomes more rapid so that the hematocrit returns to within normal limits. Once failure has occurred, total blood volume never returns to normal for the individual. The reduction in plasma usually is greatest during periods of most active diuresis.

In cases in which compensation does not occur and in which the patient remains "fixed in failure," or eventually succumbs, blood volume remains

high or increases further. If an intercurrent infection occurs during the course of compensation with a resulting relapse, the blood volume, which had come down from the high level found during the height of failure, will increase again. Recurrent failure is accompanied also by an increase over recovery levels.

The etiology of failure bears little relation to the course of blood volume. Taken as a group, patients with luetic aortic insufficiency do not exhibit as great an increase in volume during failure as do cases with rheumatic valvular disease, "chronic myocarditis," emphysema or hypertension, but the general trends of the volume in failure, compensation or relapse described above are found in all of these classifications.

It is generally recognized that the degree of elevation in venous pressure and slowing in circulation time are fair evidences of the severity of failure. In the four groups of cases with organic heart disease, referred to above, venous pressure and circulation time remained normal until failure occurred, and thereafter, as blood volume increased, there was a parallel and progressive increase in venous pressure and slowing in circulation time. During compensation venous pressure returned to within normal limits before the full reduction in blood volume occurred, but circulation time rarely returned to normal. Thus, it is safe to say that the cardiac patient with an elevated venous pressure and slow circulation time has a high blood volume.

Hypertension. Patients with essential hypertension without congestive failure comprise a group with red cell and total blood volume within normal limits.[13c, 14] In view of the markedly plethoric appearance of many hypertensives this finding is somewhat surprising and suggests that the practice of phlebotomy for the relief of hypertensive cephalalgia and dizziness cannot be justified on the basis that these symptoms are due to "too much blood."

Diseases of the Thyroid. Plasma, circulating red cell and hence total blood volume are definitely increased in hyperthyroidism [15] and the degree of elevation above normal varies directly with the increase in oxygen consumption as measured by the basal metabolism determination. This increase is less than that seen in congestive heart failure, average increase being about 10 per cent at a basal metabolic rate of + 50. The effect of iodine in the form of Lugol's solution is to reduce total blood volume and of successful subtotal thyroidectomy to restore total blood volume to within normal limits. The reduction in circulating red cell volume parallels the fall in metabolic rate on therapy.

Blood volume invariably is low in myxedema,[15] the average decrease being about 15 to 20 per cent below normal at a basal metabolic rate of — 40. If anemia is present, the blood volume tends to be lower than the average for myxedema patients without anemia. Administration of thyroid, if successful in raising metabolism, is accompanied by an increase in total volume which returns to normal simultaneously with metabolism.

Nephritis. Total blood volume is below normal in nephritis, the degree of reduction being determined by the extent of the anemia, hypoproteinemia and non-protein nitrogen retention present.[14] Anemia lowers the circulating red cell but tends to increase the plasma volume. Plasma volume varies directly with the total amount of serum albumin present in the blood stream and, therefore, tends to be low when hypoproteinemia is present. As non-protein nitrogen rises, plasma volume increases. Thus, in any phase of the disease total blood volume will reflect the influence of these factors. Since hypoproteinemia usually is more marked in subacute glomerular nephritis with edema (nephrotic syndrome) than in chronic glomerular nephritis without edema, total blood volume usually is more greatly reduced in the former stage of the disease.

In the edematous phase diuresis is accompanied by changes in plasma volume which are not related to the amount of edema lost as measured either by urinary output or weight loss but are determined by the courses of the three factors mentioned above. If therapy raises the serum albumin content of the blood, plasma volume will tend to increase, and if at the same time the circulating red cell volume increases, plasma volume will tend to fall. The relationship of these factors is such, however, that total blood volume always is below normal as long as renal function is depressed regardless of the degree of anemia present. The changes in volume that occur bear no demonstrable relationship to the presence or absence of hypertension.

Parenteral Fluid Administration. Fluids administered intravenously produce marked changes in blood volume. Immediately following the rapid intravenous injection of 50 c.c. of 50 per cent dextrose plasma volume has been observed to increase by 10 per cent or more, returning to normal in about 30 minutes. Altschule and Gilligan[16] followed the course of the plasma volume during and after intravenous infusions of normal saline, hypertonic saline and dextrose solutions in postoperative patients by means of changes in the hematocrit and serum protein concentration and in a few instances by the author's blood volume method. Fifteen hundred cubic centimeters of fluid were given in 30 minutes. The increase in volume was considerable, being as much as 30 per cent when 5 per cent dextrose was used, but less when isotonic saline was given. There was a distinct parallel between the increase in blood volume and the rise in venous pressure. Plasma volume fell to normal in about an hour. When whole blood is given[17] the effect is directly additive, all of the red cells and most of the plasma being retained within the vascular bed.

It appears that considerable caution as to the rate at which intravenous infusions are given is indicated. Rapid injection of hypertonic solutions is an heroic procedure which probably should be reserved for the emergency of shock, pending transfusion.

Anemia. The severity of any anemia commonly is judged by the determination of the hemoglobin concentration, red blood cell count or hematocrit. However, these procedures, even though carried out with the best technics,

can never give any idea of the total quantity of circulating red cells or whole blood in a given case. That the total quantity of blood must be greatly reduced in severe anemia has been appreciated by many authors, but considerable doubt has been expressed as to whether changes in red count or hemoglobin really parallel changes in total blood volume and can be safely used as therapeutic and prognostic guides.[18, 19]

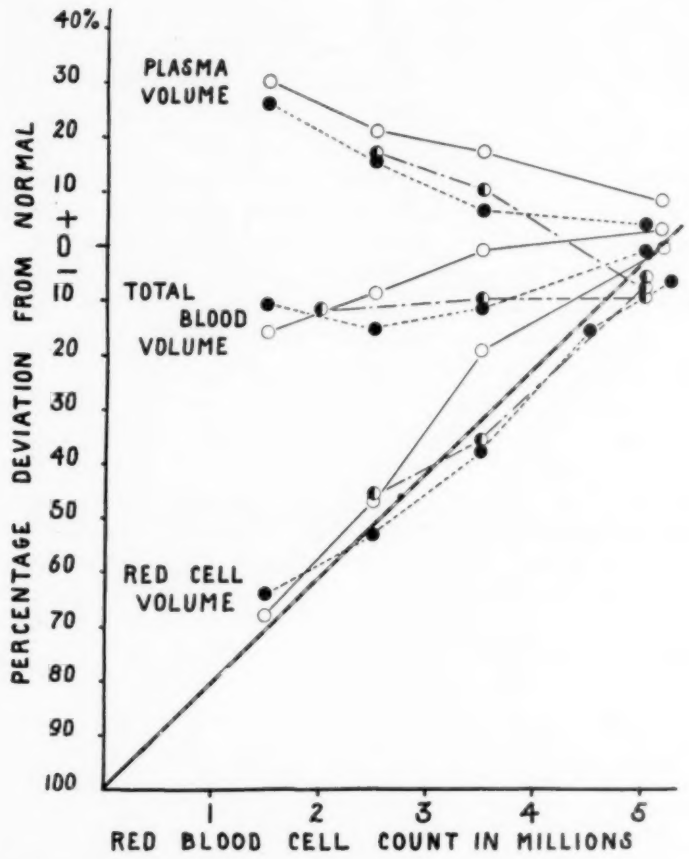

FIG. 2. Plasma, circulating red cell and total blood volume in severe anemia and during recovery. The symbols represent: primary anemia ○; secondary anemia due to all causes ●; and the anemia of nephritis ◐. The broken line represents the theoretical direct relationship between red cell count and percentage deviation from normal of the red blood cell volume. (Reproduced by permission from the Jr. Clin. Invest., 1939, xviii, 621–632.)

In the anemic patient the oxygen capacity of a unit quantity of blood is primarily dependent upon the total quantity of hemoglobin, and the severity of anemia should be evaluated in terms of the actual deficit in total circulating hemoglobin rather than the concentration of hemoglobin in a unit quantity of blood. Since total hemoglobin varies within rather narrow limits with the circulating red cell volume, the latter is also a useful criterion.

In anemia plasma volume tends to be above, circulating red cell volume greatly below, and the total blood volume below normal.[20] Except that the total blood volume tends to be below normal in chronic nephritis, regardless of the degree of anemia present, the relationship of the blood volume components to each other and to the hematocrit is practically identical in pernicious anemia, hypochromic anemia due to chronic blood loss or of unknown cause and the hemolytic anemias of familial origin, or due to malaria or drug intoxication (figure 2).

In chronic secondary anemia the deficit in circulating red cell volume may be as great as 60 per cent (and even greater in primary anemia) before alarming symptoms of impending collapse appear. During recovery, as the circulating red cell volume rises, plasma volume tends to decrease, so that total blood volume rises slowly and returns to normal only when the circulating red cell volume is fully restored, and the relationship between deficit in circulating red cell volume and hematocrit, red cell count and hemoglobin, illustrated in figure 3, holds true throughout recovery or during relapses. Thus the hematocrit and to a less extent the hemoglobin concentration and red cell count do serve as good indices of the deficit in circulating red cell volume throughout the course of anemia. It is doubtful if they are as reliable immediately following acute hemorrhage or during continued blood loss.

These facts have direct bearing on the matter of transfusion. The purpose of transfusion is not to restore blood volume completely to normal but to supply enough blood to bring a deficient volume up to the point that will tide the patient over in an emergency until his own recuperative powers can be called into play. The extent of return to normal circulating red cell volume desired depends upon whether the patient is to remain at bed rest, is to be subjected to operation, has fever, is in shock, or upon the continuance of bleeding.

From our experience it seems reasonable to assume that a deficit of over 30 per cent in circulating red cell volume constitutes a definite risk under the extreme conditions described above.

In 70 cases of secondary anemia due to all causes the circulating red cell volume was within $\pm$ 15 per cent of a line representing a theoretical direct relationship between the percentage of normal circulating red cell volume and the level of the hematocrit, red cell count and hemoglobin (figure 3). Thus, knowing the hematocrit level, it is possible (within these limits) to estimate the percentage of deficit in circulating red cell volume, and knowing the normal circulating red cell volume (figure 1), to calculate the amount of transfused blood needed to raise circulating red cell volume from a critical to a safe level in a given case. Table 1 gives some idea of the amount of red cells lacking at deficits of 60 per cent for males and females with normal total volumes of from 3425 to 6175 c.c. and the amount of whole blood needed to raise the circulating red cell volume from a 60 per cent to a 30 per cent deficit level.

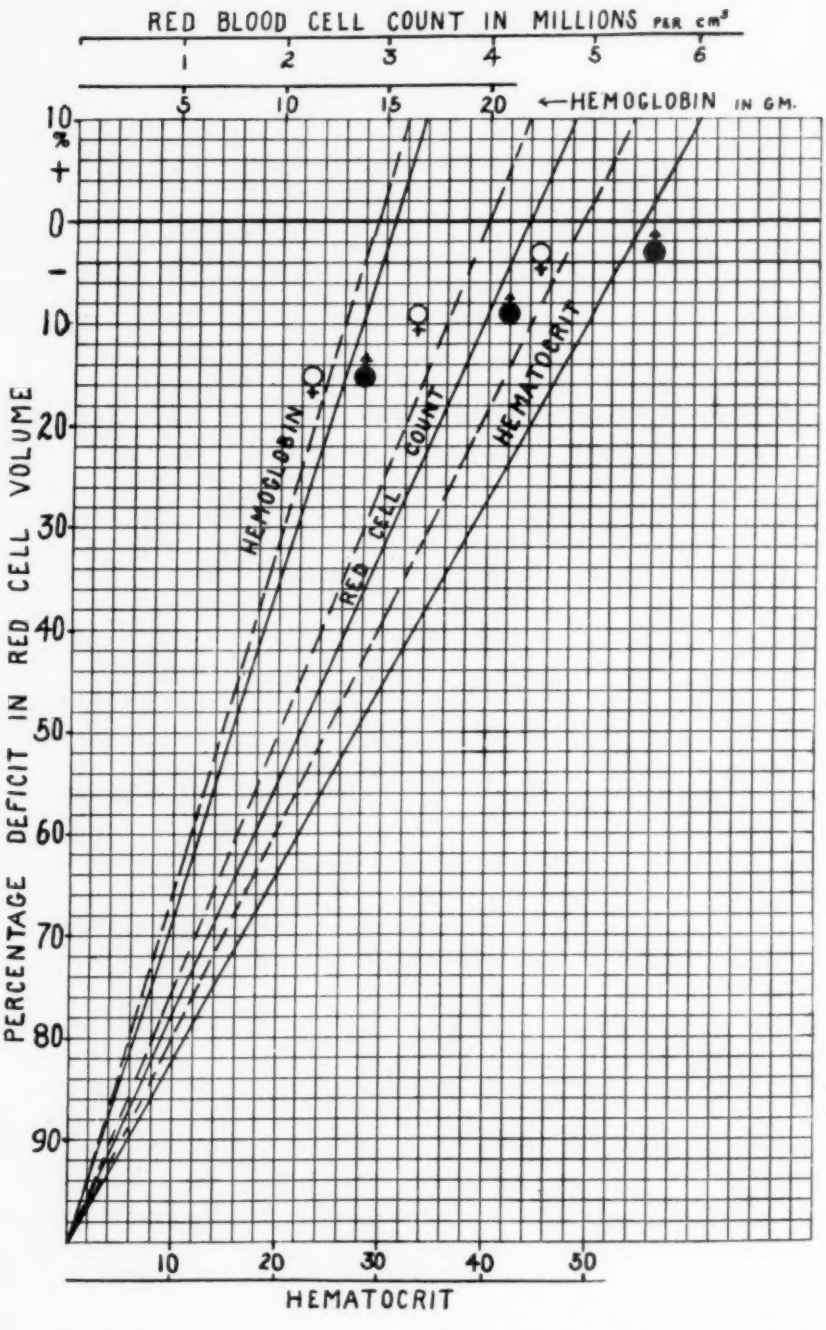

FIG. 3. The relationship between percentage deficit in circulating red blood cell volume to red cell count, hemoglobin and hematocrit at various levels of anemia. (Reproduced by permission from the Jr. Clin. Invest., 1939, xviii, 621–632.)

Thus, while a 500 c.c. transfusion may tide over a small person at rest, it may be of little value under the stress of operation, and it is evident that in larger persons, particularly males, a full liter or more may be required. It is highly probable that the unexpected and sudden peripheral vascular collapse frequently encountered post-operatively, or in burns, or in the toxemia of pregnancy is due in great part to failure to transfuse enough blood.

TABLE I

The Deficit in Circulating Red Cell Volume at Critical Levels of Anemia and the Transfusion Requirement for Males and Females

Height cm.	Sex	Normal Total Blood Volume c.c.	Deficit of 60% in Circulating Red Cell Volume * c.c.	Transfusion Requirement to Decrease Deficit to 30% †	
				Red Cells c.c.	Whole Blood ‡ c.c.
150	F.	3425	822	411	683
155	F.	3750	900	450	750
155	M.	3775	996	498	830
160	F.	3900	936	468	780
160	M.	4550	1200	600	1000
165	F.	4050	972	486	810
165	M.	4975	1313	657	1095
170	F.	4150	996	498	830
170	M.	5325	1405	703	1172
175	F.	4200	1008	504	840
175	M.	5550	1465	737	1228
180	M.	5700	1504	750	1253
185	M.	5850	1544	772	1287
190	M.	6000	1584	792	1320
195	M.	6175	1630	815	1358

* Hematocrit level of about 20.
† Hematocrit level of about 37.
‡ Assuming hematocrit of transfusion blood about 40.

Polycythemia Vera. It is well known that total blood volume is greatly above normal in this disease. As a rule, plasma volume is normal, the increase being due entirely to the huge quantity of circulating red cells.[18, 20] This increase in terms of percentage elevation above normal circulating red cell volume bears a fairly direct relationship to the hematocrit level. Plasma volume is little changed after phlebotomy, but red cell volume comes down. In our experience the most reasonable form of treatment seems to be repeated phlebotomy, the desired hematocrit level to maintain being between 40 and 50, at which most patients remain fairly symptom free.

Pregnancy. Dieckmann et al.[21] found some elevation in blood volume during the first and second trimester of pregnancy due chiefly to an hydremia, and an increased water content of the blood has been noted by Feldman et al.[22] A complete study of the changes in blood volume throughout normal pregnancy and during the puerperium has been made by Thomson et al.[23] There is a progressive increase above normal in plasma and total blood volume beginning early in pregnancy and reaching a maximum during the ninth lunar month, after which a definite decrease occurs fairly

rapidly. Thus, an increase in total blood volume amounting to almost 50 per cent at the peak has fallen to about 10 per cent above normal at term. The circulating red cell volume also increases but proportionately less than does the plasma volume, so that hematocrit, hemoglobin, and red cell count all progressively decline up to the ninth lunar month even though total blood volume is highest at this time. Total volume is essentially normal in uneventful cases 10 days after delivery.

The course of the blood volume in a group of women who had proved valvular heart disease but who went through pregnancy without any evidence of decompensation was similar to the normal group.[24]

Three facts of importance stand out. (1) The period of greatest increase in blood volume coincides with the period of greatest incidence of heart failure in pregnancy,[25] and this plethora has undoubted significance in the management of heart failure. (2) The "anemia of pregnancy" is not a true red cell deficiency but the result of hydremia. Unless the mean corpuscular hemoglobin concentration is low, it is doubtful whether any alarm need be felt or antianemic therapy used even when the hematocrit falls as low as 30. (3) Total blood volume is on an average only about 500 c.c. above normal at the onset of labor. A hemorrhage of a liter may constitute as serious an emergency on the delivery table as in the accident ward.

Anesthesia and Surgical Operations. Blood losses at operation have been carefully measured,[26, 27] and it is well known that in a normal person the amount of blood lost even in long major operations rarely is sufficient to precipitate shock. During the induction of anesthesia plasma volume tends to be diminished slightly.[28] During operation plasma volume fluctuates somewhat, there being a general tendency for it to increase as systolic pressure falls and decrease as it rises, but as a rule plasma volume is reduced from 10 to 20 per cent at the end of uneventful operations. In normal persons this reduction may be somewhat offset by an increase in the circulating red cell volume so that total blood volume may be only slightly reduced. It is probable, however, that in acute or chronic anemias no considerable reserve of red cells exists.

Severe reductions in plasma and total volume have been observed to take place during recovery from anesthesia in the "ether bed," exceeding the amounts lost at the end of operation. These losses are due to sweating and lay stress on adequate fluid replacement during recovery.

Fever. In fever induced by intravenous injection of typhoid vaccine no significant changes in total or red cell volume take place. Plasma volume may fall from 5 to 10 per cent as temperature rises but shortly afterwards is restored and remains essentially normal.[29] In recent years much attention has been given "artificial" fever. When body temperature is raised by exposure to radiant energy in any form, since the thermo-regulating mechanism remains unaffected, the mechanism increasing heat dissipation is called into play in the effort to maintain normal temperature. The peripheral

vascular bed becomes widely dilated, blood flow speeds up, blood is diverted to the skin capillaries and quantities of sweat are poured out to increase evaporative loss. Since the circulating plasma volume is determined by the rate of loss from, and absorption of fluid into the blood stream, the induction of artificial fever is attended invariably by some reduction in plasma and total volume. This reduction may be extreme (30 to 35 per cent) and precipitate peripheral vascular collapse, leading to coma and even death unless fluids are given adequately by mouth or vein.

Shock. Perhaps no other condition has been studied so extensively as shock, and it is now commonly accepted that in shock, whether "traumatic," "surgical" or "medical," the effective circulating blood volume is always reduced. The cause of the initial decline in volume, and whether in the absence of hemorrhage the quantity of blood so lost to the circulation is "pooled" in viscera or has actually escaped from the vascular bed remain questions as yet unanswered. The relationship between the degree of lowering in blood volume and the level of systolic blood pressure is another debatable question.

A review of the voluminous literature on shock is beyond the scope of this paper, but certain experimental observations may throw some light on these questions. Keeley et al.[30] produced experimental shock in anesthetized dogs by severe burns. Immediately after the burn a large reduction in plasma volume took place, and it was demonstrated that all of this fluid was lost into the burned area. On continued observation plasma volume continued to decrease gradually, but a considerable increase in circulating red cell volume occurred so that the total volume declined less than the plasma. Systolic pressure remained normal, although accompanied by increasingly rapid pulse and respiratory rate, until total blood volume was reduced about 30 per cent, when the systolic pressure suddenly fell sharply and the animal succumbed shortly thereafter. This decline in volume was accompanied by a lowering of both arterial and venous oxygen saturation, probably to be accounted for by hemoconcentration, slow blood flow due to viscosity and diminished cardiac output, the effect of acidosis on oxygen take-up in the lungs and the influence of the low CO_2 tension, resulting from acidosis, on oxygen release.

Postmortem examination of these animals revealed no evidence of "pooling." The entire gastrointestinal tract was markedly ischemic, and there had been no intestinal hemorrhage. Liver and spleen were firm and contained little blood. Lungs were dry and slightly congested. The entire body appeared dehydrated and relatively bloodless. These animals were given no fluids, and evaporation loss from the lungs was considerable.

More recent studies[31] on the effect of various types of intravenous replacement fluids in these shock preparations have shown that the administration of normal saline, hypertonic glucose, plasma or whole blood, even though they temporarily increased the blood volume with a resultant rise

in systolic pressure, did not prevent eventual collapse, if given after any considerable fall in systolic pressure had occurred. Plasma is the most effective replacement fluid, being longest retained, and decreasing the hemoconcentration and restoring the pH of the blood far better than blood or normal saline.

Other workers [32] have followed the course of blood volume in relation to peripheral flow, skin temperature and other hemodynamic measurements in patients in the terminal phase of infectious and degenerative disease. In each instance a marked decrease in plasma and total blood volume definitely preceded the eventual fall in blood pressure. Many of these patients developed peripheral edema terminally.

In shock there is first a rapid and considerable loss of plasma either into the site of injury or in a widespread manner from capillary beds. The immediate effect is hemoconcentration, slowed peripheral blood flow and decreased filling of the right heart, accompanied by vasoconstriction in the effort to maintain circulation. This vasoconstriction has the effect of maintaining systolic pressure even with a markedly reduced volume. If at this point volume is restored, recovery may take place, but if circulation remains inadequate and oxygen exchange is further interfered with, a further reduction in plasma volume may be expected due to widespread alterations in capillary permeability brought about by anoxia, and the vicious cycle so established is potentially fatal. It is, therefore, evident that the low systolic pressure clinically "characteristic" of shock is to be interpreted not as "compensatory" mechanism but as a more or less complete breakdown of compensation.

Summary

An attempt has been made to clarify certain misconceptions as to the state of the blood volume in health and disease arising from conflicting reports in the literature. No conclusions have been drawn as to the causes of changes in volume that occur in pathologic states. The characteristic behavior of the blood volume observed in normals and during various phases of congestive heart failure, essential hypertension, hyperthyroidism and myxedema, nephritis, primary and secondary anemia, polycythemia and in shock has been commented on. A method of calculating required transfusion amounts for the individual on the basis of predicted normal blood volume and level of anemia has been described. Appreciation of these states and changes may offer the clinician a sounder basis for the evaluation of diagnostic and therapeutic procedures in the conditions studied.

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ACUTE OCCLUSIONS OF THE PERIPHERAL ARTERIES; CLINICAL ANALYSIS AND TREATMENT *

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No more dramatic episode exists in medicine, than the sudden onset of an arterial occlusion. In fact, the onset is so characteristic that the condition is seldom overlooked. Unfortunately, however, the proper therapy is often too long delayed.

I am therefore presenting an analysis of 31 cases † of acute closure of the peripheral arteries to call attention to certain clinical features that require emphasis, and to show that extremities can be saved when proper conservative measures are instituted. I shall also attempt to show that the loss of life in individuals who are properly treated is not due to the acute arterial lesion per se, but rather to the basic disease that existed before the embolism or thrombosis occurred. If one can prevent the formation of gangrene, the chances of saving the affected limb and thereby prolonging life are proportionately greater.

General Considerations

An acute occlusion of a peripheral artery consists either of an embolism or a thrombosis. An analysis of the numerous causes of these conditions would constitute an essay in itself, and is outside the scope of this paper. Suffice it to say, that there are very definite criteria to determine whether one is dealing with an embolism or a thrombosis.

When a sudden arterial obstruction occurs in a patient who shows evidence of peripheral vascular disease and who presents no signs of a focus from which emboli might originate, that obstruction is considered thrombotic in nature. On the other hand, when an acute closure of an arterial pathway takes place in an individual who presents no evidence of peripheral vascular disease, but exhibits definite signs of cardiac disease, that closure may be diagnosed as embolic, particularly so, when the individual is in the younger age group.

Heart conditions of particular importance in the diagnosis of embolism are: (1) auricular fibrillation, (2) mitral stenosis, (3) acute or subacute bacterial endocarditis, (4) infarction of the wall of the left ventricle with thrombus formation, and (5) paradoxical embolism with patent foramen ovale. Pulmonary phlebitis in lung infections is another predisposing cause

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† Twenty-seven patients are from the private and ward services of the Bronx Hospital and four are from the author's private practice, outside the hospital.

of embolism. An embolus may also arise from a thrombosis of the wall of another artery, or from an aneurysm above the site of lodgement.

It is important to remember that emboli are seldom large enough to occlude the larger arteries, such as the aorta and common iliacs, except perhaps at the bifurcation of these vessels, where the lumen is suddenly narrowed, and a saddleback anatomic arrangement exists. In arteriosclerotic arteries, partial or complete thrombosis occurs when the atheromatous intima ulcerates through, and emboli may be caught at that particular point; so that even with an embolic background, the real etiology of sudden closure at any point of an artery may be thrombotic in character.

Etiology

Age. There were 13 cases diagnosed as embolism. Two were 25 and 28 years old respectively, four were between 40 and 50, and seven over 50 years of age. Of the 18 cases diagnosed as thrombosis, one was 47 years of age, six were between 50 and 60, and eleven were over 60 years of age. The embolic group therefore, was definitely younger. There was no difference in the age of either sex in the embolic or thrombotic group.

Sex. The embolic group compromised five male and eight female patients. The thrombotic group had an equal number of each sex. Sex, therefore, was no factor in etiology.

Diabetes. In the embolic group there were four patients with diabetes, all four being females. In the thrombotic patients, 10 had diabetes, three males and seven females. It seems therefore, that diabetes prevailed more in females than in males, 11 out of 14 diabetics being females.

Fibrillation. Nine cases of embolism had fibrillation. Eight of these definitely fibrillated prior to the acute accident. In one case, no mention was made as to the time of onset of fibrillation. Of the 18 thrombotic cases, seven presented signs of fibrillation, five definitely before, and one after the accident. In one instance the time of onset of fibrillation could not be determined. In the embolic group, therefore, fibrillation was present before the accident in 61 per cent of the cases, and in the thrombotic group in only 28 per cent of patients.

Underlying Disease Status

Embolism. The two patients who were 25 and 28 years old, had subacute and acute bacterial endocarditis, respectively. One patient had coronary thrombosis, one had arteriosclerotic heart disease, three had hypertensive heart disease, and six had rheumatic heart disease.

Thrombosis. One patient had coronary thrombosis, four had hypertensive heart disease, six had arteriosclerotic heart disease, three had rheumatic heart disease, and four had arteriosclerosis obliterans. From these data it may be seen that the most frequently associated condition in the majority of cases was heart disease; and as will be seen later, it was this

condition, and not the peripheral vascular state, that determined whether the patient survived.

Anatomical Considerations

Vessels Involved. The aortic bifurcation was involved in two patients, once in embolism and once in thrombosis. The external iliac vessels were affected in five cases, once in embolism and four times in thrombosis. The femorals were occluded in eight cases, five times in embolism and three times in thrombosis. The popliteal was involved in ten cases, four times in embolism and six times in thrombosis. The anterior tibial was occluded in three instances, all being thrombosis. There was one thrombosis of the axillary artery, one embolism of the small vessels of the hand, and one embolus to the digitals of the big toes. There was really no specificity of vessel involvement either in embolism or thrombosis.

Multiple Arterial Involvements. There were four cases of embolism with multiple arterial occlusions and only one case of thrombosis with more than one simultaneous arterial obstruction.

Onset of Gangrene. In only eight of the 13 cases of gangrene could the date of onset of gangrene be determined. The one case of aortic bifurcation obstruction developed gangrene of the thighs, legs and feet in 24 hours. Two cases of external iliac artery occlusion developed gangrene in two and 15 days respectively. Gangrene set in from one day to three weeks in four cases of femoral obstruction, while one case of embolism to the digitals of the big toe showed gangrene in 24 hours.

Vessels involved in cases of gangrene were the aortic bifurcation in one case, the external iliac in two cases, the femoral in seven cases, the popliteal in two cases, and the digitals to the toes in one case. It seems, therefore, that the femoral artery occlusion produced gangrene most frequently, but one must remember that six of these seven cases were treated prior to the onset of gangrene by individuals not trained in the conservative therapy of acute occlusions.

Symptoms

The symptoms of an acute obstruction to the arterial supply of a limb come on suddenly, and no differentiation between embolism and acute thrombosis can be made from the symptoms alone. The first symptom in 23 of the 31 cases (76 per cent), was a sudden onset of sharp pain in the affected limb. It was present in eight of the embolic and 15 of the thrombotic cases. Six cases complained of a sudden onset of numbness (four embolic and two thrombotic). One patient with thrombosis had a gradual onset of pain, and one patient with embolism complained at first of "pins and needles" sensation. Other symptoms followed rapidly in order: sudden pallor with grayish cyanosis in severe cases; coldness of the limb; loss of sensation and motion of the distal part of the extremity.

Signs

The extremity was pale or gray cyanotic in color; felt cold, below the site of obstruction; the superficial veins were collapsed; sensation in the distal part of the limb was diminished or lost; and in high occlusions, the function of the distal joints was lost. The pulsations of the main arterial vessels were absent, at least below the site of occlusion. Often for a period of hours, days, or weeks, the pulsations of vessels proximal to the affected area were also absent. This loss of pulsation occasionally extended to the opposite member, and was due to the associated reflex vasomotor spasm.

Laboratory Findings

The evaluation of fever, white blood count with differential, and sedimentation time was difficult, due to the fact that the majority of patients had preëxisting cardiac failure, polycythemia, or infection. Often too, the case was admitted weeks after the acute closure and the findings were therefore of no importance.

List of Cases

Acute Occlusions of the Peripheral Arteries

Case	Age	Sex	Diagnosis	Complications	Diabetes	Therapy	Gangrene	Amputation	Died after Accident	Living
62731	25	F.	E. R. Fem.	R.H.D., Sub. B.	0	0	2 da.	0	16 days	
75317	61	F.	E. R. Fem.	H.H.D.	+	0	1 da.	+	3 mos. after discharge	
58865	50	F.	E. L. Pop.	R.H.D., A.F.	0	0	16 da.	+	?	?
49840	50	F.	E. R. Fem., R. Brach.	H.H.D., A.F.	+	0	1 da.	0	10 days	
61974	64	M.	T. R. Fem.	A.S.H.D.	0	0	2 wks.	+	?	?
62216	60	F.	T. R. Fem.	A.S.H.D., A.F.	+	0	in 3 wks.	+	?	?
60229	63	F.	T. R. Pop.	Cor. Thromb.	+	0	6 da.	+	30 mos. after discharge	
36801	73	F.	T. L. Fem.	H.H.D., A.F.	0	0	1 da.	0	2 days	
97686	41	M.	E. R. and L. Pop.	R.H.D., A.F.	0	Pavaex	0	0		11 mos.
75457	28	M.	E. L. Pop.	R.H.D., Ac. Bact.	0	Pavaex	0	0	10 days	
97813	46	M.	E. L. Fem., R. Ulnar	R.H.D., A.F.	0	Pavaex	0	0		10 mos.
102949	46	M.	E. R. Pop.	R.H.D., A.F.	0	Pavaex	0	0		5 mos.
84300	56	F.	E. L. Fem.	R.H.D., A.F.	+	Pavaex	23 da.	0	26 mos. after discharge	
75752	60	F.	E. Digitals to toes	H.H.D., A.F.	0	Pavaex	1 da.	0		33 mos.
88805	67	F.	E. R. Pop., L. Ant. Tib.	A.S.H.D., A.F., H.H.D.	0	Pavaex	0	0	5 days	

E. refers to embolism, T. to thrombosis, R.H.D. to rheumatic heart disease, H.H.D. to hypertensive heart disease, A.S.H.D. to arteriosclerotic heart disease, A.S.O. to arteriosclerosis obliterans, A.F. to auricular fibrillation.

These cases are brought up to date as of December 30, 1939.

LIST OF CASES (*Continued*)

Case	Age	Sex	Diagnosis	Complications	Diabetes	Therapy	Gangrene	Amputation	Died after Accident	Living
M. R. Dr. F.	55	F.	E. L. Ext. Iliac	R.H.D., A.F.	+	Pavaex	0	0	4 days	
S. S. Dr. W.	46	M.	Bifur. E. Aorta	Cor. Thromb.	0	0	1 da.	0	4 days	
103387	47	F.	T. Bifur. Aorta	R.H.D., A.F.	0	Pavaex	0	0	16 da. after discharge	
104101	61	M.	T. L. Ext. Iliac	A.S.O.	0	Pavaex	0	0		4 mos.
105918	56	F.	T. R. Pop.	R.H.D., A.F.	+	Pavaex	0	0		2 mos.
106857	53	M.	T. Ant. Tib.	A.S.H.D.	0	Pavaex	0	0		1 week
82403	67	F.	T. L. Pop.	A.S.H.D., H.H.D.	+	Pavaex	0	0	?	?
91909	68	M.	T. L. Ext. Iliac	A.S.O.	+	Pavaex	0	0		17 mos.
Dr. A. I.	51	M.	T. L. Ext. Iliac	A.S.O.	0	Pavaex	2 da.	+		8 mos.
98872	52	M.	T. Small vessel R. hand	A.S.H.D., A.F., H.H.D.	+	Pavaex	0	0	18 days	
96367	70	M.	T. L. Ant. Tibial	Polycythemia, Chr. Bronchitis	+	Pavaex	0	0		13 mos.
C. A. Dr. Kohlenberg	65	M.	T. R. Axillary	A.S.H.D., Nephritis	0	0	0	0	12 days	
103686	64	F.	T. R. Ext. Iliac	A.S.H.D., A.F., A.S.O.	+	0	15 da.	0		4 mos.
93712	66	F.	T. R. Fem., L. Pop.	A.S.H.D.	+	Pavaex	0	0	3 days	
92860	57	F.	T. R. Ant. Tibial	R.H.D., A.F.	+	Pavaex	0	0		16 mos.
71283	52	M.	T. R. Pop.	A.S.H.D.	0	Pavaex	0	0	33 mos. after discharge	

The blood Wassermann and Kahn tests were done in 21 patients and all proved negative.

No oscillometric tracings were taken for fear of further trauma to the damaged peripheral vascular system.

In nine cases tested by means of thermal reflex vasodilatation [1] the affected limb gave little or no response. The reaction in the opposite limb depended on the state of the peripheral circulation.

Intra-arterial diodrast injections were done in several cases, and the block was demonstrated, but no conclusions were drawn from this procedure. (The reason for this is that the mere insertion of a needle into an artery may produce a spasm of the vessel, and only when patency of the vascular system is visualized, can the result of this procedure be accepted without hesitancy.)

CONSERVATIVE THERAPY

The conservative therapy of acute arterial occlusions by the use of alternate suction and pressure was reported by Herrmann and Reid [2] in

1933. Landis and Gibbon [3] in the same year also showed the effects of this form of treatment on the blood flow to the lower extremities. Linton [4] in 1937 reported 60 per cent successful results in sudden arterial closures by the use of "pavaex." His results compared more than favorably with those of embolectomy published by Lund.[5] Linton divided 44 cases of acute arterial occlusions into three groups in order to evaluate the effect of different forms of treatment. In the group which received no therapy, the limb was saved in 29 per cent of the cases. In the group treated by embolectomy a similar successful result was obtained in 33 per cent. Suction pressure therapy was used in the last group and the limb affected was saved in 60 per cent of the cases. In 1932 Cook and Brown [6] measured the vasodilating effects of alcohol on the peripheral arteries, while de Takats [7] in 1936 emphasized the value of papaverine, intravenously, to allay the pain and arterial spasm incidental to acute closures.

In the conservatively treated cases of this series, I used a combination of the foregoing measures, and adhered to the following routine. The patient was put to bed and was given one-half grain of papaverine intravenously as soon as possible. He was covered with wool blankets; warm water bottles were placed in the axillae when the lesion was in the lower extremities; and whiskey was given in one ounce doses, three times daily.

The patient was seen by a member of the peripheral vascular department as soon as possible, and the affected limb was placed in a suction pressure apparatus. The apparatus was adjusted so that during the negative phase, the skin of the limb would either become pink, or the superficial veins would fill: during the positive phase the skin of the extremity would pale, or the superficial veins would collapse. If the patient could stand it, he would receive six to twelve hours of continuous treatment. On the second day he would receive four to six hours, and then the treatment would gradually be reduced to two hours daily. We tried in most cases to give a minimum of 100 treatment hours.

The contraindications to the use of suction pressure therapy are, first, pain during therapy; second, infection; and third, edema. Our treated cases presented neither infection nor edema, and in only one instance was pain during treatment a factor in the cessation of therapy. It was usually high negative pressure that caused pain and the negative pressure could often be diminished to the point where treatment could be tolerated.

Results of Treatment

In discussing the results of treatment, I shall divide this series into the untreated and the conservatively treated groups. The untreated group comprised eight cases seen between October 1933, and July 1936. There were four embolic and four thrombotic patients. Of the four embolic cases, all developed gangrene. The femoral artery was affected in three instances, one of which was amputated at mid-thigh. All three died in ten days to

three months. The fourth case, involving the popliteal artery, was amputated at mid-thigh, left the hospital alive, but no follow-up was obtained. In the four cases of thrombosis, all developed gangrene. The femoral artery was affected in three instances, two of which were amputated at mid-thigh. The two amputated cases left the hospital and no follow-up was obtained. The third femoral artery case died in two days. The popliteal artery was involved in the fourth case. This patient had a mid-thigh amputation, and died two and one-half years after discharge from the hospital.

Of the eight cases, therefore, all had gangrene, and five were amputated. Of the five amputated cases, three could not be followed, one died three months after discharge, and one died two and one-half years after discharge. The three non-amputated cases died in two to 19 days.

Of 23 cases treated conservatively since July 1936, there were nine embolic and fourteen thrombotic patients.

Of the nine embolic cases eight were treated with suction pressure therapy. These comprised occlusions of two femorals, four popliteals, one external iliac, and one case of the digitals to the toes. There were only two instances of gangrene, and in no case was it necessary to amputate. Four patients are alive after five to 33 months; three patients died of cardiac failure in four to ten days after the accident. The eighth patient was discharged from the hospital and died 31 months later. The ninth case, that of the patient who did not receive pavaex therapy, was an instance of coronary thrombosis followed by arterial obstruction at the aortic bifurcation. He had been treated outside the hospital with a heat lamp, and had developed extensive gangrene. This patient died four days after the accident.

Of the 14 thrombotic cases, 12 were treated with suction pressure therapy. These comprised one case of obstruction of the aortic bifurcation, one of the femoral, three of the external iliac, three of the popliteal, three of the anterior tibial, and one of the small vessels of the hand. There was only one instance of gangrene, and this occurred in an external iliac involvement. This was the only case necessitating a mid-thigh amputation. The two cases not treated by suction pressure therapy were: (1) a thrombosis of the axillary artery, and (2) a thrombosis of the external iliac artery. The former did not develop gangrene, but the case died 12 days after the accident. The latter patient, still alive, had developed moist, gangrenous lesions of the toes, and so suction pressure therapy was contraindicated.

Of the 12 patients treated with suction and pressure, seven are alive; (six are alive after four to 17 months; one is a recent anterior tibial lesion of one week's duration, and is doing well); three died four days to 33 months after leaving the hospital; one died in three days while in the hospital, and one could not be followed up after discharge. Including the two cases not treated with suction pressure therapy, there are eight known living, five known dead, and one with no follow-up.

Of the entire 23 cases, therefore, five developed gangrene, but there was only one amputation. Eleven patients are known to be alive after four to 33 months, and one is alive one week after the accident and is doing well. Ten are known dead, and in one there was no follow-up. There was no essential difference between the results in the embolic and those in the thrombotic patients.

In comparing the data of the untreated and conservatively treated groups, it is only fair to omit three cases from the conservative series: those involving the axillary, the small vessels of the hand, and the digitals to the toes. The results in untreated cases then give the following figures: a loss of limb in 62.5 per cent of the cases, and a known mortality of 62.5 per cent. In cases conservatively treated there was loss of limb in only 5 per cent (one case) and a mortality rate of 40 per cent.

Stay in Hospital

The length of stay in the hospital in the cases of this series was dated from the time of admission to the time of discharge if the arterial lesion was present on admission. Otherwise it was dated from the day the accident occurred on the ward to the time of discharge. In the eight cases of the untreated series, the length of stay was two to 60 days, with an average of 32.4 days; and in the amputated patients an average of 45.8 days. In the conservative treatment series, the length of stay for the embolic group was 26.2 days, and for the thrombotic group 24.1 days, an average of 25 days. For the suction pressure group the average hospital stay was 25 days, an average of seven days less than that of the untreated group, and 20 days less than the amputated group.

Time of Onset of Therapy

In the 16 patients who did not develop gangrene, pavaex therapy was instituted from two hours to five days after the accident, and in one case, 21 days after the occlusion. In the three cases where gangrene set in, therapy was started 15 to 72 hours after the obstruction occurred. In the four cases that died in the hospital, treatment was started in eight to 16 hours after the occlusion, so that in this series the actual time of onset of pavaex therapy was not the deciding factor as to whether the patient would live, or gangrene set in.

Total Hours of Treatment

In the 16 of the 18 cases that survived hospital stay, the number of treatment hours with suction pressure therapy was from four to 160. The period of treatment varied according to the state of the limb, the restlessness of the patient, and the demand of the bed by the hospital. Pain was relieved almost immediately in the majority of cases with the use of suction pressure therapy. Function of the distal parts returned about 24 to 48 hours in the

popliteal cases. In one external iliac case, there was a loss of function of the ankle (this was the case that was amputated in two weeks due to gangrene). In one femoral case there was a permanent loss of function of the big toe. Sensation returned at the same time as function. Warmth of the limb returned considerably later, sometimes in weeks and sometimes not at all.

Return of Pulsations

A consideration of this phenomenon entails the evaluation of reflex vasospasm. It is a known fact that when a lesion occurs in an artery (or vein), a spasm may occur in that vessel, proximal to the site of the lesion. This spasm may extend for varying distances up the vessel, and may extend even to the vessels of the opposite limb. In the case of the lesion of a small artery to the hand, no pulsations could be felt in the entire upper extremity of the involved side. Nine hours after the accident the brachial pulsation could be felt. The radial artery pulsation returned in three days, but the ulnar could never be felt. Palpable pulsations returned in six other cases; the case of partial thrombosis of the bifurcation of the aorta presented a return of the right femoral pulsation in one day, the left femoral in two days, and both popliteal and dorsalis pedis artery pulsations in eight days. At post mortem, 44 days later, the aortic bifurcation was found totally occluded by thrombus.* One case of embolism to the lower part of the femoral showed a return of pulsation in the inguinal region in two days. In one case of popliteal thrombosis, the femoral pulsation returned in four days. In one case of anterior tibial thrombosis, the posterior tibial pulsation was felt 93 days after the accident. In another anterior tibial thrombosis the popliteal pulsation was felt in 24 hours, and the posterior tibial in 48 hours. In a third case of anterior tibial thrombosis, the posterior tibial pulsation returned in 38 hours.

From the foregoing facts one may assume that if any pulsation will return, it will usually return within four days, and rarely later.

Causes of Death

There were 15 known dead patients, eight in the embolic and seven in the thrombotic group. All eight embolic cases died of cardiac failure. Four of the thrombotic group died of cardiac failure; one of cerebral embolism; one of cerebral thrombosis; and one died at home of undetermined cause. All the deaths were, therefore, not due to the peripheral vascular condition of the extremity, but rather to the underlying disease.

Summary

Twenty-nine cases of major and two of minor arterial occlusions are presented. Criteria are given for the differentiation of embolism from thrombosis. The embolic cases were younger in age. Sex was not shown

* Personal communication with Dr. Alfred Angrist, Pathologist of the Jewish Memorial Hospital.

to be a factor in the causation of occlusion. Diabetes was an associated condition in females more often than in males. Fibrillation was a frequent precursor of embolization, but not of thrombosis. Heart disease was the underlying condition in 100 per cent of the cases of embolism and 78 per cent of the cases of thrombosis. There was no specificity of vessel involvement, either in embolism or thrombosis.

The symptoms and signs of sudden occlusions are described.

Acute closures below the popliteal artery seldom caused gangrene. Therapy involving watchful waiting in eight out of 31 cases, gave a loss of limb in 62.5 per cent and a known mortality of 62.5 per cent. Conservative therapy in 23 cases gave a saving of limb in 95 per cent. The hospital stay of conservatively treated cases was 20.8 days less, on the average, than that of the untreated group.

Conclusion

The use of alternate suction pressure therapy combined with vasodilating procedures is an efficient method for the treatment of acute peripheral arterial thrombosis and embolism. The adoption of these measures of treatment produces a high percentage of saving of limbs, a low percentage of gangrene, and a lowering of the mortality rate.

I wish to express my appreciation to Dr. A. Goldman, Dr. E. Koffler, Dr. H. Schumer, and Dr. S. P. Sobel of the medical staff for their coöperation in the study of the above cases.

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THE TREATMENT OF BARBITURATE INTOXICATION WITH SPECIAL REFERENCE TO PICROTOXIN; A REPORT OF 20 CASES *

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THE clinical use of picrotoxin in combating acute barbiturate intoxication is sufficiently new that an experience with 20 cases of this type, observed during the last year and a half, may prove of value. In recent years, the taking of large quantities of barbiturates of various kinds has become an increasingly popular method of attempting suicide. In all of the cases to be described, the barbiturate was taken with suicidal intent, and the patients were seen and treated on the medical services of St. Vincent's Charity and Glenville Hospitals, in Cleveland.

Although Browne [1] discovered, in 1875, that picrotoxin protected rabbits against five to eight times the minimal lethal dose of chloral hydrate, the present clinical use of picrotoxin was stimulated, in 1931, by the experimental work on barbiturate poisoning by Maloney and his associates [2, 3] at the University of Wisconsin. Since then, the clinical use of picrotoxin in barbiturate poisoning has been reported by Arnett,[4] Koppanyi, Linegar and Dille,[5] Kline, Bigg and Whitney,[6] Gower and Van de Erve,[7] Bleckwenn and Masten,[8] Rovenstine,[9] Lovibond and Steel,[10] Anderson [11] and others. Lovibond and Steel, in 1939, reported that 24 cases had been described in the literature, and that in 17 instances, the patient had recovered as the result of treatment with picrotoxin.

CASE REPORTS

In six instances in the series of 20 cases of barbiturate poisoning, picrotoxin was not used, because the intoxication was mild and responded to other methods of treatment.

Case 1. A young woman, aged 20 years, was seen at Charity Hospital three hours after she had ingested 12 amytal tablets. She was in a semi-comatose state, but could be roused by painful stimuli. Her temperature was 97° F.; the pulse rate, 74; the blood pressure, 110 systolic, 74 diastolic; the respiratory rate was 16 per minute. Gastric lavage was carried out immediately and one ounce of magnesium sulphate was left in the stomach. A total dose of four c.c. of coramine also was administered. She recovered promptly, and was discharged from the hospital the day after admission.

Case 2. A Jewish girl, aged 19 years, was admitted to Charity Hospital about 24 hours after she had taken nine tablets of barbital. She was stuporous and semi-comatose and her speech was incoherent, although all reflexes were intact. She had been under treatment for an hysterical neurosis for some time before this incident. She recovered from the toxic effects of the barbiturate without special treatment of any kind.

* Read at the Cleveland meeting of the American College of Physicians, April 3, 1940.

Case 3. A young woman, aged 20 years, took "three pink and four white sleeping powders," and was admitted to Glenville Hospital a few hours afterward. On admission, she was lethargic and her speech was incoherent. The blood pressure was 100 systolic, 80 diastolic; the pulse rate was 120; and the respirations, 10 per minute. Pupillary reflexes were present. Gastric lavage was done, and caffeine and sodium benzoate were administered. No other treatment was necessary.

Case 4. A married woman, aged 41 years, was admitted to Glenville Hospital about 12 hours after she had ingested 25 one and one-half grain phenobarbital tablets. The patient was an obese woman, who was comatose, and displayed no reactions to external stimuli. Her temperature was 99° F.; the pulse rate, 80; and the respirations, 18 per minute. All tendon reflexes were absent, but the pupils were of normal size, and reacted to light. The lungs were clear and the heart normal.

A solution of sodium chloride and glucose was administered intravenously. The patient also received caffeine and sodium benzoate, and 1 c.c. of coramine. No other measures were necessary to arouse her from coma.

The next two cases are of interest, in that the ingestion of the barbiturate was accompanied by large quantities of alcohol.

Case 5. A married woman, aged 38 years, decided to commit suicide because her husband had left her. She drank as much liquor as she could stand, and then tried to find some bichloride of mercury. Failing that, she took seven nembutal capsules. She was admitted to Charity Hospital a few hours later in an excited, talkative and boisterous condition. Physical examination revealed nothing abnormal, except diminished tendon reflexes. The pupils were normal in size, and reacted to light. The patient refused to take anything by mouth, and chloral hydrate was administered by rectum. It is interesting that, in the presence of the alcoholic intoxication, the seven capsules of nembutal did not even induce sleep.

Case 6. A single man, aged 35, had been drinking heavily and taking white sedative tablets. About two hours before he was admitted to Glenville Hospital, he took 20 or more of the tablets. When he was examined, he was unconscious, and appeared cyanotic. He was breathing stertorously, but his pulse was regular, and of good volume. The pupils were of normal size. He could not be roused by painful stimuli, but gastric lavage caused him to thrash about. A 10 per cent glucose solution (500 c.c.) was administered intravenously, and two doses of apomorphine, 1/30 grain each, were given. In addition, oxygen was administered intranasally. After partial recovery, sedatives had to be employed to quiet the patient. He recovered without incident, and was dismissed from the hospital in six days.

In the following case, no picrotoxin was used, because it was not available at the time. This case was one of the earliest in the series, and indicates that other stimulants, such as caffeine and sodium benzoate and coramine are ineffective in combating severe barbiturate intoxication.

Case 7. A single woman, aged 22 years, was admitted to Charity Hospital several hours after ingestion of an unknown quantity of barbital. She was emaciated, comatose and cyanotic, and had gurgling respirations. The pulse rate was elevated to 160 with regular rhythm. The blood pressure was 190 systolic, 80 diastolic. The pupils were contracted and reacted sluggishly to light. The throat was filled with a frothy fluid. The chest was resonant, but the sounds were obscured by bubbling rhonchi. The corneal reflex was present, although all tendon reflexes were absent. Treatment consisted of gastric lavage, suction of mucus from the throat, and the administration of caffeine sodium benzoate, coramine and atropine. No picrotoxin was used. The patient lived 36 hours after admission to the hospital. Before death,

the temperature rose to 105° F., and the pulse rate was 160. The respiratory rate was 50 per minute.

In the next two cases, which also resulted in death, some picrotoxin was used, but in insufficient dosage. Hence these cases should not be regarded as failures of picrotoxin therapy.

Case 8. A married woman, aged 21 years, was admitted to Charity Hospital in a comatose condition. No history was obtainable, but it is probable that she had taken phenobarbital, although the quantity and the time of ingestion could not be ascertained. When she was examined, there was no cyanosis, dyspnea, or acute distress. The temperature was 98° F.; the pulse rate, 96; and the blood pressure, 110 systolic, 50 diastolic. The lungs were entirely clear. The patient was not considered to be in serious condition, and coramine, caffeine, strychnine and sodium chloride solutions were administered. The following day, however, she was still in coma, and the temperature was elevated to 104° F., with a pulse rate of 150. The blood pressure had fallen to 90 systolic, 30 diastolic. The administration of picrotoxin was then instituted, in doses of 6 mg. and 3 mg., at hourly intervals. The patient failed to rally, however, and died the following morning. It is probable in this case that the dosage of picrotoxin was not sufficient, and that too long a time was allowed to elapse before its administration.

Case 9. A single woman, aged 21 years, was admitted to Glenville Hospital early in the morning after she had taken 91 one and one-half grain phenobarbital tablets before retiring the night before. She was comatose, but not cyanotic, and had shallow respirations. All reflexes were absent, and the pupils were greatly contracted. The lungs were clear, and the heart appeared normal.

Concentrated glucose solution was given immediately, and then a 5 per cent solution of sodium chloride and glucose was given continuously by vein. One dose of picrotoxin, 9 mg., was given, but no more was available at the time. Twelve hours after admission, an extensive urticaria developed, and adrenalin was used in an effort to relieve this. Atropine, coramine and caffeine also were administered, but the patient sank rapidly, and died the following morning, 22 hours after admission. The patient had had a psychoneurosis for some time, and her mother also was mentally ill.

In the next two cases, metrazol was used experimentally, as a substitute for picrotoxin. In the first of these, no other treatment was necessary. In the second case, picrotoxin had to be resorted to, but the patient's condition was complicated by pneumonia and she did not recover.

Case 10. A single woman, aged 24, was brought into Charity Hospital three hours after she had taken 18 seconal tablets. The patient displayed no cyanosis, and the pupils were dilated but reacted to light. The pulse rate was 96; the respirations, 12; and the blood pressure 120 systolic, 80 diastolic. Gastric lavage was carried out immediately, and respirations ceased as the tube was withdrawn. Coramine (2 c.c.) was given immediately and artificial respiration was instituted, until breathing was reestablished. During the next four hours, the patient received 25 c.c. of metrazol, which brought her out of coma, and she made an uneventful recovery.

Case 11. A married woman, aged 39 years, was admitted to Glenville Hospital about 16 hours after she had ingested 75 one and one-half grain phenobarbital tablets. She was comatose and cyanotic, and her throat was filled with mucus. All tendon reflexes were absent; the pupils were greatly contracted, but exhibited a slight reaction to light, and the corneal reflexes also could be elicited. Numerous bubbling râles were heard in both lungs; these made the heart sounds inaudible. There was tenderness in the lower abdomen, pressure over this area eliciting grunting. The patient's tem-

perature was 101° F.; the pulse rate, 120; respirations, 28; and the blood pressure 90 systolic, 60 diastolic. A little later, the blood pressure had dropped to 60 systolic, 30 diastolic.

During the first 24 hours, the patient was treated with metrazol (12 c.c.). She had a clonic spasm after one dose of 3 c.c. She also received five doses of atropine, 1/150 grain, and two injections of concentrated glucose solution. At the end of this period, the temperature had risen to 105°; the pulse rate was approximately 160; the respirations, 52; and the blood pressure ranged between 100 and 60 systolic, and 50 to 30 diastolic. The patient was in deep coma, and displayed no reactions of any sort.

The second day, sulfapyridine therapy was instituted, and 60 mg. of picrotoxin were given, within a period of 20 minutes. The patient then responded to painful stimuli, and the corneal reflexes could be elicited. She aroused sufficiently to vomit some coffee-grounds material. Her temperature was still 105.2°. Infusions of sodium chloride and glucose solution were administered and an additional quantity of 90 mg. of picrotoxin was given in a period of 20 hours, but the patient failed to rally, and died at the end of this time.

In addition to the preceding case, the barbiturate intoxication was complicated by pneumonia in five other cases. In four of these, giant bullous lesions, ranging in size from 2.5 to 10 cm. in diameter, developed on the skin in areas subjected to pressure.

Case 12. After losing his W.P.A. job, about four o'clock one afternoon, a married, white man, aged 26 years, took 40 grains of amytal. He was admitted to Charity Hospital about five hours later in a comatose condition. His blood pressure was 120 systolic, 60 diastolic; the temperature, 104°; the pulse rate, 100; and the respirations, 24 per minute. All reflexes were absent, and there was urinary and rectal incontinence. The lungs displayed no dullness, but there was much mucus in the throat which caused bubbling respirations.

Gastric lavage was carried out five or six times, and the administration of picrotoxin was started about an hour after admission. The corneal reflexes could be elicited an hour later, but these disappeared again during the night, although the administration of picrotoxin was continued. The temperature remained elevated, and the respiratory rate increased to 38 a minute. The following morning, the patient was still in deep coma, and the corneal reflexes were still absent. These returned about 20 hours after treatment was begun. A 5 per cent solution of glucose was given intravenously, the picrotoxin was continued, and sulfapyridine also was administered. Milk, water, and coffee were introduced through a nasal tube. The patient regained consciousness about 36 hours after admission. He remained sleepy, but could be roused to talk rationally. A roentgenogram disclosed evidence of broncho-pneumonia, and the sulfapyridine was continued for three days. A week later, the patient had entirely recovered, and was discharged from the hospital.

Case 13. A single woman, aged approximately 30 years, was taken off the Detroit-Cleveland boat, unconscious, and was brought to Charity Hospital. In her luggage a 100 tablet bottle of phenobarbital was found, from which about 80 tablets were missing. When she was first examined, the patient was in deep coma. All tendon and ocular reflexes were absent. The pupils were round and equal and did not react to light. Gurgling râles were audible in the lungs, and the respiratory rate was thirty-two. Later this was diminished to fourteen. The pulse rate was 120 and the blood pressure, 85 systolic, 52 diastolic. There was evidence of peripheral stasis, and there were localized erythematous wheals on the hands and arms.

Gastric lavage was carried out, and the administration of picrotoxin was begun immediately. The following day, the patient appeared in critical condition; the tem-

perature had risen to 105.5°, and the blood pressure to 140 systolic, 100 diastolic. On several dependent portions of her body lesions were discovered which appeared to be subcutaneous hematomas. These later broke down, leaving open ulcers. The largest of these lesions was on the sacrum. Large quantities of glucose and sodium chloride solutions were administered, and caffeine sodium benzoate and sodium salicylate were given, in addition to the picrotoxin. At this time there was considerable edema of the entire body and of the tongue, and a mottled discoloration, due to circulatory stasis. The throat was filled with mucus, which could not be removed readily by suction.

The second day after admission, the skin lesions developed on the elbows and heels, but the patient had less mucus in the throat and appeared to be slightly improved. The therapy was continued intravenously, but the congestion in the chest increased, and she died on the fourth day after admission.

Case 14. A married man, aged 37 years, was admitted to Charity Hospital, in coma. No history was obtainable at the time, but the patient later admitted that he had taken 40 veronal tablets. Because of intense muscular rigidity, an injection of 50 per cent glucose solution, with 3¾ grains of amytal, was administered intravenously. Complete relaxation of the muscles followed immediately. The pupils were of regular size, but reacted sluggishly to light. All other reflexes were absent. The throat contained mucus, and there were numerous râles in the chest, which obscured the heart sounds.

Because no history was available at the time of admission, the diagnosis of barbiturate poisoning was not made until about 24 hours afterwards. The administration of picrotoxin was then started, and sulfapyridine was given for the pneumonia. At this time, the patient's temperature was 105°; the pulse rate, 150; respirations, 45; and the blood pressure 140 systolic, 80 diastolic. Coffee, and sodium chloride and glucose solutions were given, in addition to the picrotoxin.

The characteristic skin lesions appeared in the sacral region, and on the shoulders and feet, on the second day after admission. By the fourth day, the patient was gradually emerging from coma. A week after admission, he was still stuporous, but could be roused to talk rationally. He was out of bed on the tenth day, but had a foot drop and a weakness of one hand, which was considered to be caused by a peripheral neuritis, and vitamin B therapy was instituted. He remained in the hospital for about two weeks after this, to receive supportive treatment. When he was dismissed, he was in good condition, except for mental depression and anorexia.

Case 15. A single man, aged 21 years, was at work on June 30, 1939. The following day, his landlady saw him in bed and thought he was sleeping. The next day he was still in bed, unconscious and foaming at the mouth, so a physician was called, and the patient was sent to Charity Hospital. He was undernourished and so comatose, dyspneic and cyanotic as to appear moribund at the time of admission. His temperature was 105.5°; the pulse rate was 180; the respirations, 60 each minute. All reflexes were absent, the pupils were contracted and did not react to light. There was limited expansion of the chest on the left side and coarse, bubbling râles throughout both lungs. The heart rate was extremely rapid and the sounds were indistinct.

At first, the patient's condition was attributed to severe pneumonia, and sulfapyridine and caffeine sodium benzoate were administered. Within 12 hours, and after learning that he probably had taken 150 grains of barbital, picrotoxin was started.

Two days after admission, red areas appeared over the sacrum, on both heels and on the inner surface of the left foot where it had pressed against the right foot. The redness increased on the sacral areas, and dark, blister-like lesions appeared on the feet, which proceeded to ulcerations. The ulcers healed with the formation of keloids which were still present when he was dismissed from the hospital, about six weeks after admission. Abscesses also formed in the gluteal region which had to be drained.

Within a week after admission, the pneumonia had subsided somewhat, the patient's temperature was reduced, he was rational, and able to take fluids by mouth.

Several weeks later, when he was able to be up and about, he complained of pain in his feet and legs. This was considered to be peripheral neuritis, and vitamin B was prescribed. A little later, there was atrophy of the two medial lumbrical muscles and the hypothenar muscles of the right hand, with loss of pain sensation over the entire surface of the little finger and the medial half of the ring finger, with contracture of the ring and little fingers. The patient was examined by a neurologist who made a diagnosis of impairment of multiple motor and sensory peripheral nerves.

This case is instructive in showing that picrotoxin may be effective even in the most extreme degrees of barbiturate intoxication. The patient had been neglected for at least 36 hours after ingestion of the barbiturates and appeared near death from pneumonia at the time treatment was initiated. This patient also had the troublesome skin lesions and peripheral neuritis, probably as the result of malnutrition, aggravated by lack of food intake occasioned by the barbiturate poisoning.

Case 16. A man, aged 30 years, was brought into Charity Hospital about 18 hours after he had ingested 48 grains of nembutal. He was comatose and cyanotic, and all reflexes were absent. The pupils were of pin-point size. The lungs were resonant and displayed a few rhonchi.

Gastric lavage was carried out immediately and therapy with sulfapyridine and picrotoxin was instituted. The following day, several large blebs which appeared to be filled with gelatinous material developed on the ankles and hips. A culture of material from these lesions showed the presence of *Staphylococcus albus.* Within 48 hours, the patient was fully awake and talking intelligently. The Wassermann reaction was four plus, and the patient previously had undergone treatment for syphilis. About 15 years before, he had also fractured his skull in a fight, following which he had had meningitis and had been in a hospital for about seven weeks.

In four cases, the severe drug intoxication was not complicated by pneumonia or skin eruptions. All these patients were treated with picrotoxin, and all recovered.

Case 17. A young woman, aged 20 years, was admitted to Charity Hospital 45 minutes after ingestion of 72 grains of sodium amytal. She was already comatose, and all tendon, corneal and pupillary reflexes were absent. The pupils were of pin-point size. Her temperature was 96.3°; the pulse rate was 92; and the respirations, 14 per minute. Picrotoxin (156 mg. in solution) was administered intravenously within 24 hours. Fifty-four hours after admission, the patient was sitting up in bed, taking nourishment by mouth, and talking intelligently.

Case 18. About an hour before her admission to Glenville Hospital, a young woman, aged 20 years, ingested 48 one and one-half grain sodium amytal tablets. She was unconscious and all reflexes were greatly diminished. The pupils were of pin-point size, but exhibited a slight reaction. The temperature was 96°; the pulse rate, 90; the respirations, 16; and the blood pressure 124 systolic, 82 diastolic. No picrotoxin was available at the time she entered the hospital, so during the first 12 hours she was treated with strychnine, caffeine and sodium benzoate, and sodium chloride and glucose solution intravenously. Twelve hours after admission, the administration of picrotoxin was started, and 162 mg. in solution were used in the next 24 hours. Within two days, the patient was able to sit up in bed, to take nourishment by mouth, and to answer questions intelligently. She made an uneventful recovery, and was dismissed from the hospital a few days later.

Case 19. A woman, single, aged 27 years, was brought into Glenville Hospital about 12 hours after she had taken 60 grains of ipral-calcium. She was comatose, and all tendon reflexes were absent. The corneal reflexes could barely be elicited and the pupils were greatly contracted, although they still reacted to light. The respirations were shallow, but the lungs were clear. The heart was enlarged, and there was mitral stenosis, with regurgitation. A history obtained later disclosed that the patient had known for three years that she had "leakage of the heart."

Gastric lavage was carried out, and the administration of picrotoxin begun immediately. The total quantity administered was 162 mg., 144 mg. in the first 24 hours, and 18 mg. in the second 24 hours. In addition, sodium chloride and glucose solution (6,000 c.c.) was administered during the first 24 hours. The patient was still very lethargic, but talking incoherently 48 hours after admission. Seventy-two hours had elapsed before she could be roused to talk normally.

Case 20. A married woman, aged 45 years, had been depressed and suffering considerably with insomnia, for which she had been taking phenobarbital. One afternoon she took 24 tablets, and was admitted to Glenville Hospital a few hours later in a deeply narcotized state. She was moderately obese and her skin was flushed, but not cyanotic. All reflexes were sluggish, and the corneal and swallowing reflexes were absent. The pupils were contracted, but reacted to light. The lungs were clear, and the respiratory rate was 28 per minute. The pulse rate was 120, and the heart was not enlarged. The blood pressure was 120 systolic, 80 diastolic.

Gastric lavage was carried out, with magnesium sulphate solution, two ounces of which were left in the stomach. Sodium chloride and glucose solution was administered intravenously. The patient also received oxygen intranasally, and five doses of caffeine sodium benzoate, in addition to the picrotoxin, which was started as soon as she entered the hospital. She received a total dosage of 126 mg. in 42 hours, and made a satisfactory recovery. Her depression was thought to be a menopausal psychosis.

Discussion

In reviewing this series of 20 cases of barbiturate poisoning, certain facts emerge quite clearly, and are worthy of comment.

There is a considerable margin of safety in the use of barbiturates. No extreme intoxications occurred with quantities less than 12 times the usual dosage. The length of time from the ingestion of the drug to the beginning of treatment is extremely important. Even large doses may not cause serious consequences if gastric lavage is carried out within a few hours.

Patients who display a severe degree of bulbar paralysis, with hyperpyrexia, tachycardia, and shallow respirations are doomed to die unless some powerful stimulant is employed immediately. Because of the depression of respiratory function, and the resulting atelectasis, the attending physician must be on the alert to detect the first signs of pneumonia. If there is any evidence of pneumonia, sulfapyridine therapy should be instituted at once. Three patients in this group, with extensive pneumonia and severe barbiturate poisoning, recovered.

In severe cases of barbiturate intoxication, ordinary stimulants are ineffective. These include caffeine, strychnine and coramine. The only cases in which they seemed effective were those of mild or slight degrees of poisoning, and these patients might have recovered without any special treat-

ment. Glucose and sodium chloride solutions administered intravenously, and supplemented in some instances by injections of salyrgan have an important place in the treatment of patients with barbiturate intoxication. In the presence of cyanosis, oxygen is helpful. In our experience, this has been administered only by the inhalation method.

Metrazol has been tried in two cases in this series. One patient recovered with no other treatment. In the other case, picrotoxin was substituted, but the patient died.

Picrotoxin is the drug of choice in treating barbiturate intoxication. It is a powerful stimulant, and in our hands there have been no ill effects from its use. To obtain the best results, it should be instituted promptly if the reflexes are abolished, and should be given intravenously at the rate of approximately 1 c.c. or 3 milligrams each minute until the corneal reflexes reappear and the patient responds to painful stimuli. Thereafter it should be repeated at hourly or at least two-hourly intervals in a dosage sufficient to keep the corneal reflexes active. This requires approximately 3 to 6 mg. an hour, depending on the degree of depression. Whenever the patient is allowed to lapse into a severe depression for several hours, his chances of recovery are greatly lessened.

The occurrence of the skin lesions described in several of the cases was at first rather puzzling. I had not had any experience with skin lesions in barbiturate poisoning before I began using picrotoxin, and hence wondered whether they might be due to the latter drug. For that reason, the dosage of picrotoxin was decreased deliberately in one or two cases, until it was ruled out as the cause.

Various allergic manifestations due to barbital have been described in the literature.[12-16] These consist of a fine erythematous rash which simulates scarlet fever, and urticarial eruptions, with itching. I have also observed two instances of an influenza-like allergy following the use of theominal (theobromine plus luminal). Vesicular eruptions have also been reported, but I am unaware that anyone else has reported the giant bullous lesions observed in these cases. These vary in size from 2.5 to 10 centimeters. The interesting fact is that they occur only at the points of pressure, but some are well developed within 24 hours after admission. Dr. Clyde Cummer and Dr. C. J. LaRocco have made a special study of these skin manifestations, and plan to report them from the dermatologic viewpoint.

The fact that one patient developed severe peripheral neuritis, and that another showed similar, though less severe, symptoms, emphasizes the importance of nutritional deficiency in these cases. When a patient whose diet has been inadequate is deprived of essential foods and vitamins for several days, because of coma resulting from barbiturate intoxication, clinical signs of a serious deficiency may develop.

It must be remembered, of course, that many of these patients are psychoneurotic and that there is little point in preventing their suicide unless the

proper psychiatric and social treatment is furnished afterwards. Some patients, it is true, are normal mentally, but have had such poor living environment that they are driven to destroy themselves. In these cases, investigation by a social worker, followed by encouragement and the kind of help they need, may restore them to a useful place in the community.

Summary

Twenty cases of barbiturate intoxication as the result of attempted suicide, observed during the past 18 months at St. Vincent's Charity and Glenville Hospitals, in Cleveland, are reported, with special reference to the use of picrotoxin in treatment.

Fifteen patients recovered and five died. Three of the five deaths, however, can not fairly be counted as failures of picrotoxin therapy. In one case, no picrotoxin was used, because it was not available at the time, and another patient received only one dose, for the same reason. In the third case, the quantity of picrotoxin used was insufficient because the patient had not appeared to be in serious condition. In the remaining two fatal cases, the treatment was adequate, but unavailing, because of the severity of the intoxication and widespread pneumonia.

Serious poisoning does not result unless approximately 12 times the usual dose of the drug is ingested.

Ordinary stimulants are ineffective, except in mild cases.

Picrotoxin is effective in the treatment of this condition, and no ill effects have been observed following its use. It must be administered in dosages sufficient to keep the patient in a slightly restless condition. To allow the patient to lapse into deep coma for a period of hours greatly lessens the chance for recovery.

Prompt lavage of the stomach, followed by the injection of glucose and sodium chloride solutions, for diuresis, is an important part of the treatment.

In a number of cases in this series, skin lesions resembling giant bullae occurred in pressure areas. So far as is known, lesions of this type have not been reported previously.

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CIRCUMSCRIBED AND ISOLATED BRONCHIECTASIS *

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Sanatorium, Texas

BRONCHIECTASIS is generally thought of as a widespread and diffuse disease involving the greater part of a lobe, or perhaps several lobes. We have been unable to find references to limited or circumscribed dilatations in American literature and know of but two cases which have been reported in foreign publications.[2] These two cases showed, one a dilatation involving the axillary branch of the right lower lobe and the other a dilated pectoral branch of the right upper bronchus. Both were of a saccular variety. It was not stated whether or not the contralateral side had been injected.

In searching the files of bronchograms on over four hundred patients at the State Tuberculosis Sanatorium, we have encountered a surprisingly large number of cases in which bronchiectasis was limited in extent. After using the most rigid criteria to establish the fact that the bronchiectasis was limited, we have found six cases that seem sufficiently distinctive to report and two others that we consider as borderline for reasons given below.

The basis upon which we excluded 10 cases was either that the contralateral side for some reason had not been injected or that filling seemed inadequate to rule out the possibility that some adjacent branches might be dilated. The reason for our insistence upon injection of a contralateral side is that very frequently when bronchiectasis is present to an advanced degree on one side, there may be a few branches showing a slighter dilatation on the opposite side. Neither roentgen-ray nor physical examination is sufficiently infallible to permit one to say that the other side is normal: the fact is not established without injection.

Naturally it is also necessary that the injection be sufficiently extensive to include all adjacent branches over a considerable portion of the lung, since obstruction is fairly common in the disease. This should also take care of the objection that the injection of oil revealed only a portion of the disease present.

CASE REPORTS

Case 1. Mrs. M. L. K., white female, 31 years of age, had pneumonia in 1934 and has had sinus disease for years. No other respiratory history. Has never raised any blood but ever since the pneumonia has been expectorating about 5 c.c. of mucoid material in the course of 24 hours. Râles were heard in the right base near the anterior axillary line. Ordinary sputum examinations and Pottenger concentrations were negative for tuberculosis. The ordinary roentgen-ray was of little aid. Bronchogram showed a varicose dilatation of two or three branches of the basillaris medius, the location being just proximal to the costo-phrenic angle (figure 1).

* Received for publication November 9, 1939.

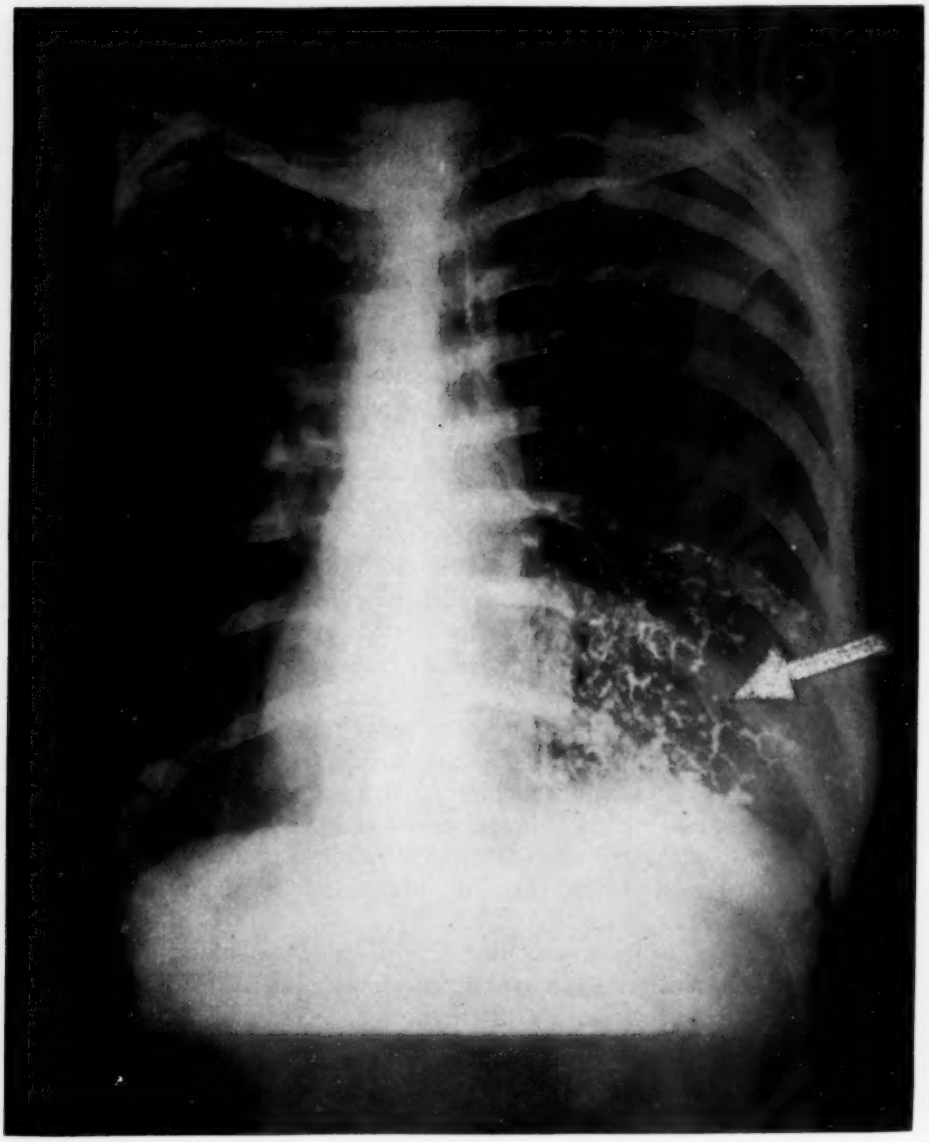

FIG. 1. Mrs. M. L. K. Note dilatation, indicated by arrow, in the direct continuation of the lower lobe bronchus.

Case 2. Miss I. H., white female, 37 years of age. She had pneumonia at the age of eight and "influenza" in 1931 and 1936. Since the last attack she had expectorated slightly but continuously, but had never produced any blood. Râles were heard in the right cardio-phrenic angle. Her sputum here was of a mucoid character with a little pus and ranged from 15 c.c. to complete absence. The roentgen-ray showed a moderate increase in markings in the costo-phrenic angle on the right. Since several sputums and Pottenger concentrations were negative, she was injected with iodized oil. Bronchogram: Saccular dilatation of two or three branches of the basillaris ventralis (figure 2).

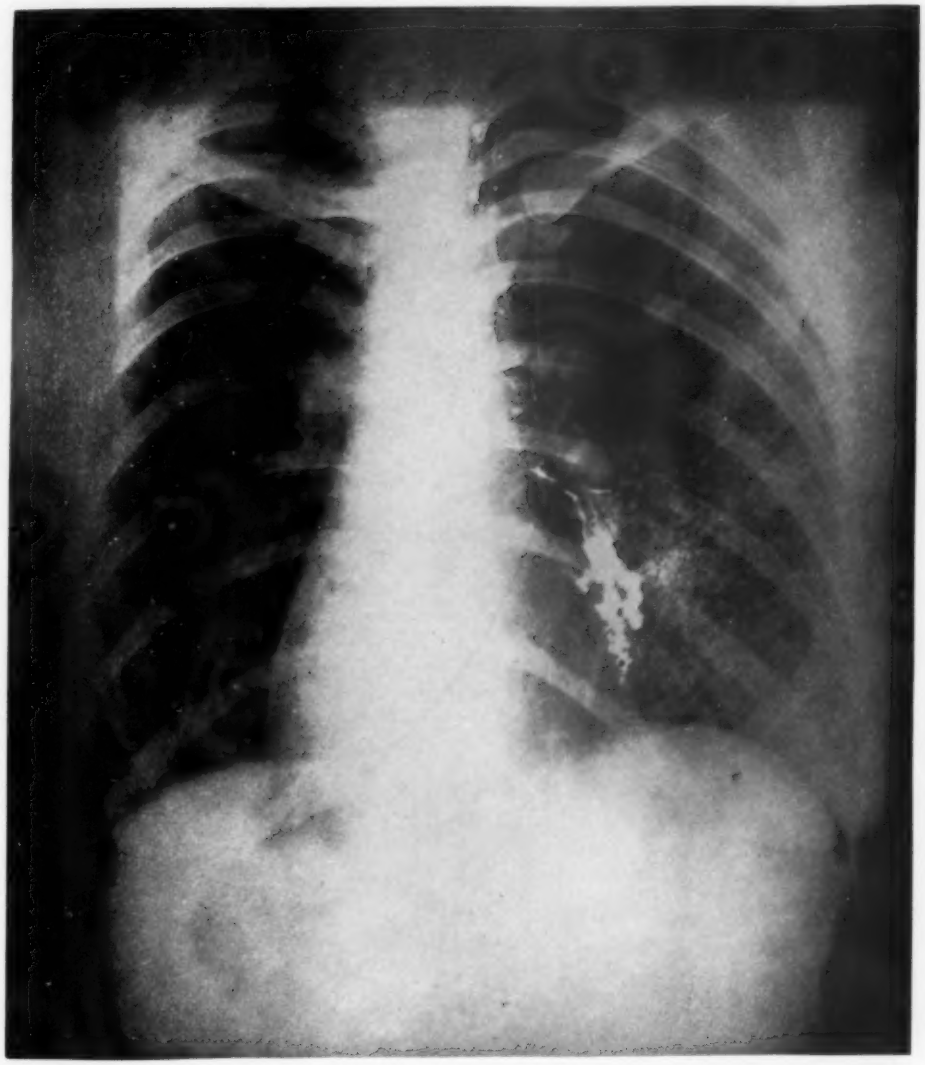

FIG. 2. Miss I. H. Dilatation limited to cardio-phrenic angle.

Case 3. Miss E. S., white female, 17 years of age, had been perfectly well until an attack of "influenza" in 1937. No other respiratory history. Since 1937 she had produced as much as 15 c.c. of sputum fairly regularly each day and on occasions it had been lightly streaked with blood. Râles were heard in the right base. The sputum being negative on ordinary smear and Pottenger concentration, but persisting around 15 c.c. of mucoid material daily, it was decided to inject her, since the routine plate was not significant. Bronchogram: Varicose dilatation of a few branches of the basillaris ventralis in the right cardio-phrenic angle (figure 3).

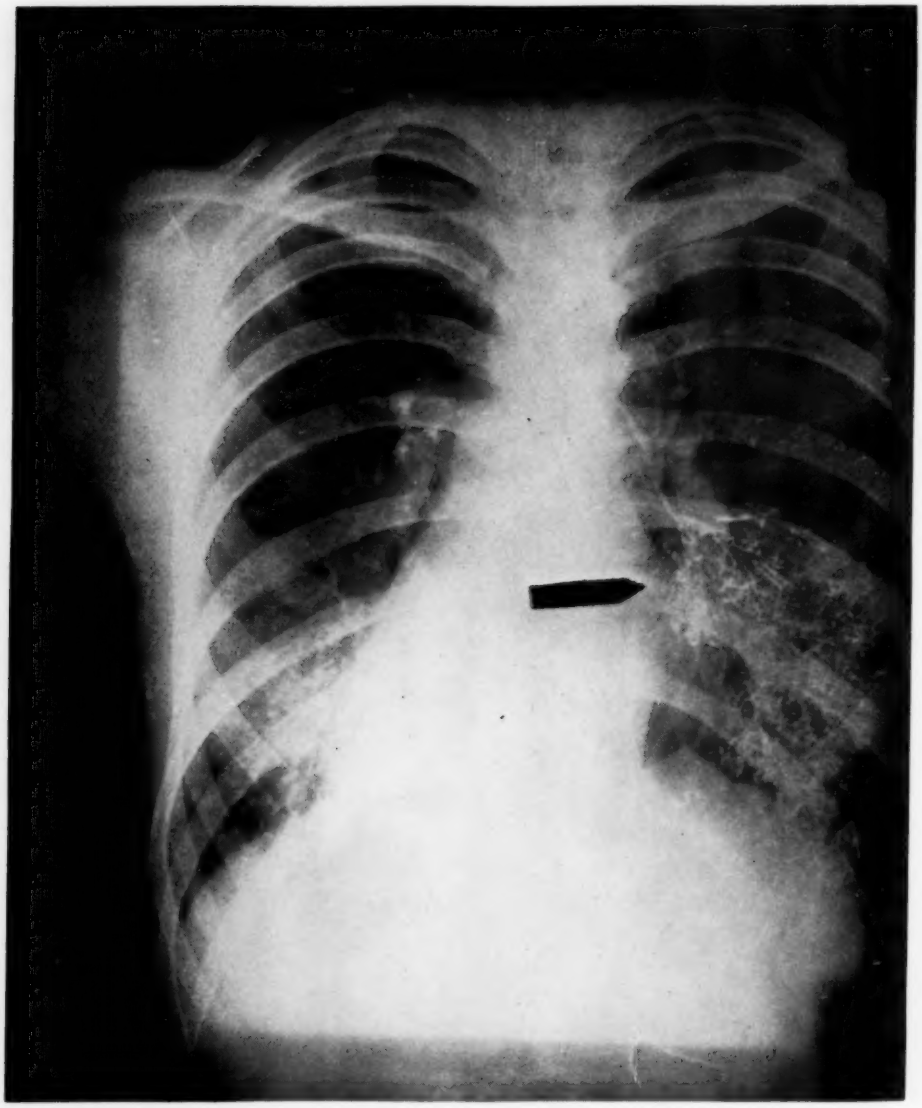

FIG. 3. Miss E. S. Dilatation limited to cardio-phrenic angle.

Case 4. R. D. H., white male, 26 years of age, claimed that he had been raising about 30 c.c. of sputum daily since two years of age. He had had a recent small hemorrhage. Had "influenza" and pneumonia in 1935, and had had sinus trouble for the past two years. No râles were heard. Repeated sputums were negative on smear and concentration, but since he continued to expectorate about 5 c.c. of muco-pus daily and since his routine plate showed no significant changes, he was injected. Bronchogram: Varicose dilatations of the basillaris medius near the costo-phrenic angle on the right (figure 4).

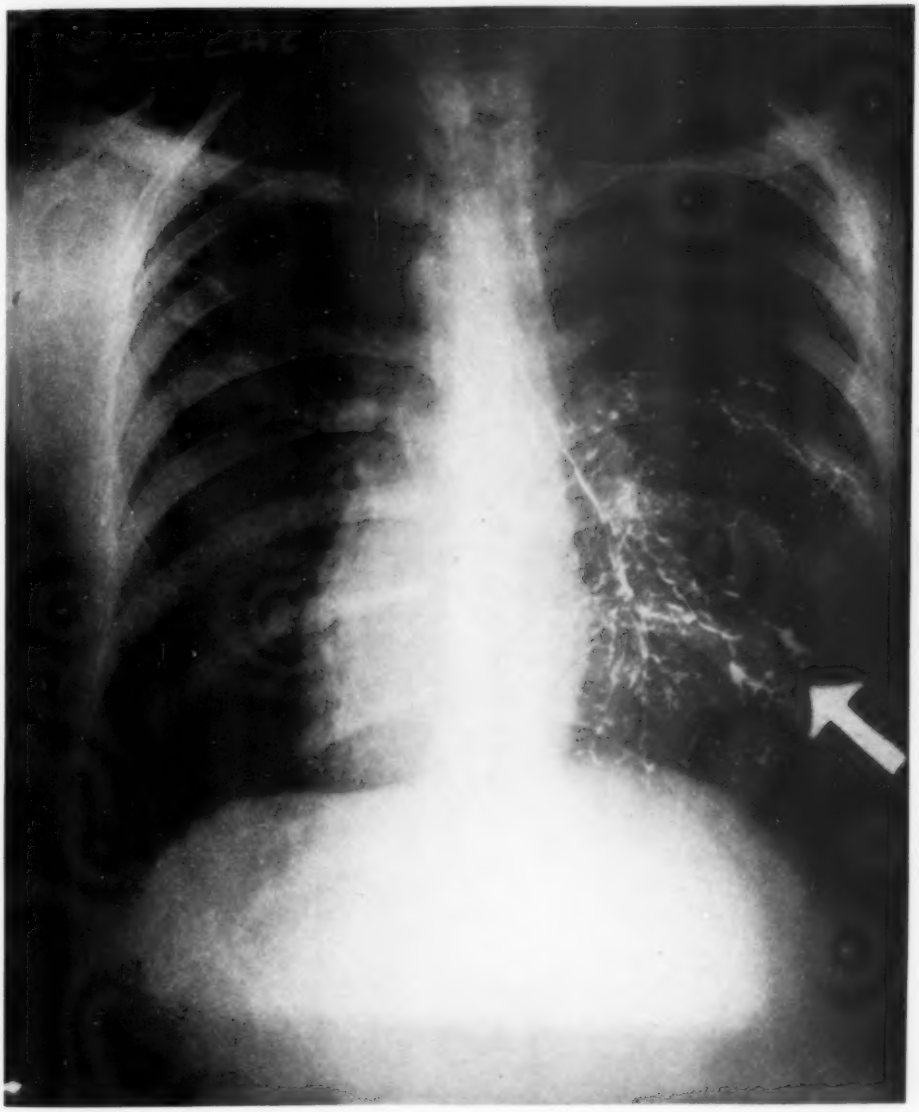

FIG. 4. R. D. H. Varicose dilatations limited to the basillaris medius branches near costo-phrenic angle.

Case 5. Mrs. S. J. R., white female, 36 years of age. Claims to have had "influenza" every winter for 10 years. Had pneumonia at the age of three. Denies expectoration or hemoptysis. Râles were heard in the right base. Sputum was completely absent during her residence in the sanatorium. Roentgen-ray plate showed nothing suggestive. Bronchogram: Cylindrical dilatation and obstruction of the direct continuation of the lower lobe bronchus, terminating in small bud-like dilatations in the costo-phrenic angle area (figure 5).

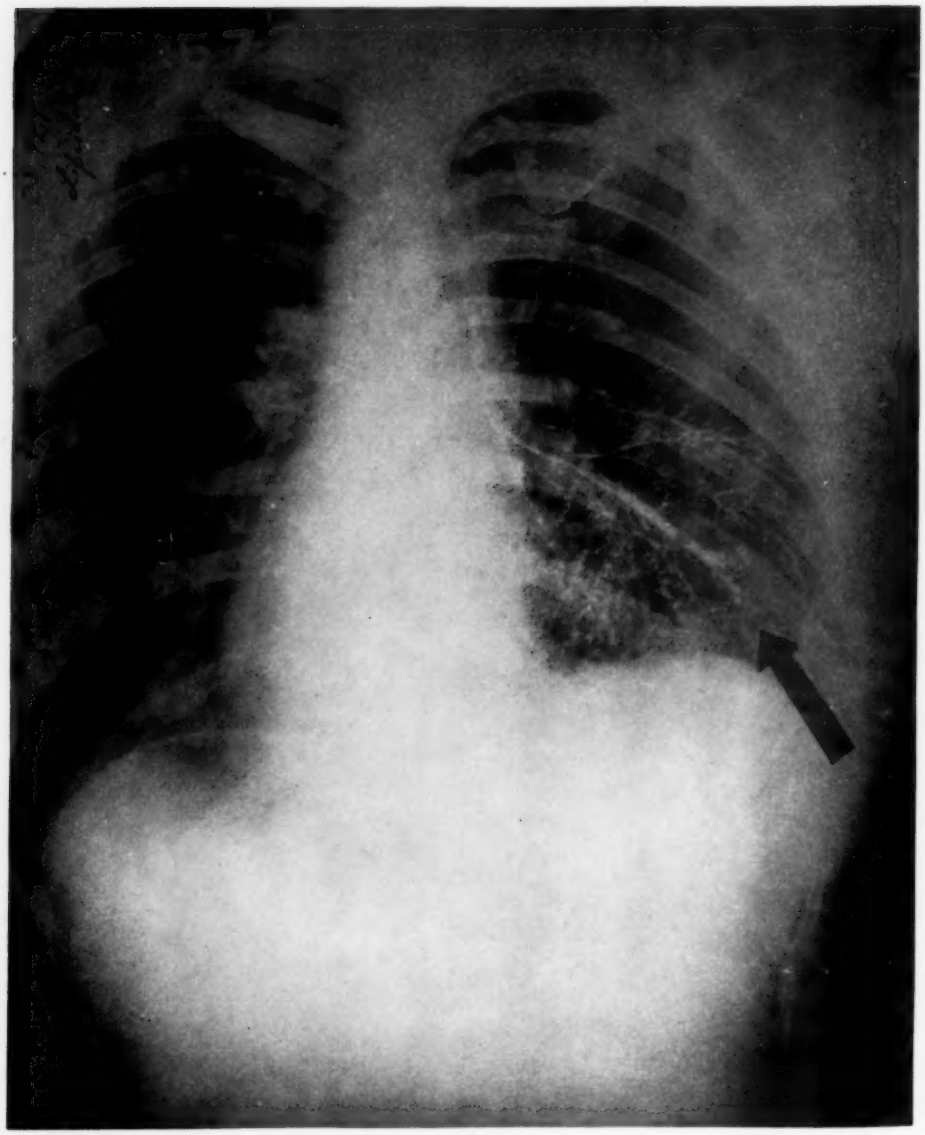

FIG. 5. Mrs. S. J. R. Dilatation in direct continuation of lower lobe bronchus with small saccules in bronchioles.

Case 6. G. A. S., white male, 29 years of age. He gave absolutely no history except of slight chest pain for the past two years. The examiner reported hearing basal râles bilaterally. Sputum remained around 15 c.c. of mucus in 24 hours and was negative on repeated smear and concentration. The routine plate revealed nothing important. Bronchogram: Cylindrical dilatation of cardio-phrenic branches of the basillaris medius, right (figure 6).

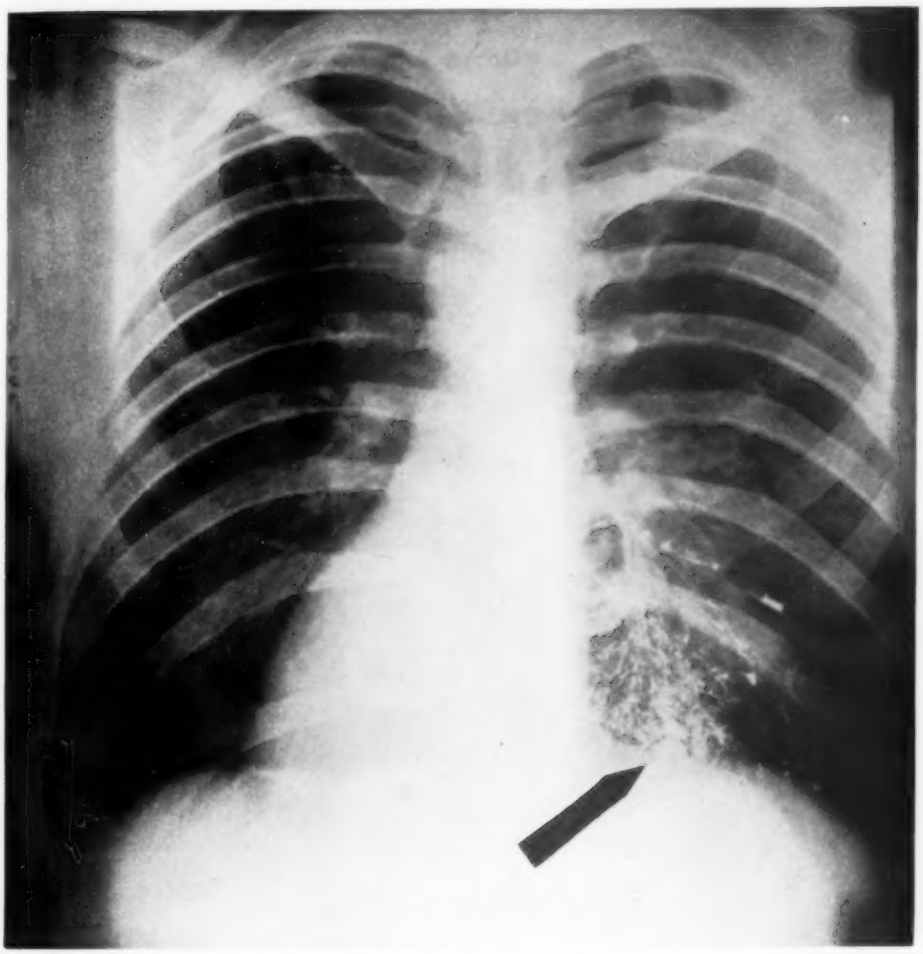

FIG. 6. G. A. S. Dilatations in the cardio-phrenic angle.

Case 7. D. D. W., white male, 54 years of age, had hemorrhage of about 120 c.c. recently and has been expectorating about six months. He had pneumonia in 1917 and 1932 and "influenza" in 1936. In 1928 he had an abscess of the left lung which was treated medically by postural drainage and from which he apparently made a good recovery. His sputum here averaged about 30 c.c. of mucoid material daily and was consistently negative for tubercle organisms. The roentgen-ray plate showed a few strands radiating out into the left periphery about half-way up from the diaphragm. Bronchogram: Saccular dilatations of axillary branches of basillaris medius on the left (figure 7).

Case 8. C. D. A., white male, 29 years of age, had pneumonia in 1935. For about two months has been expectorating about 30 c.c. daily. In addition he has had a small hemoptysis of less than 30 c.c. The sputum here was definitely purulent and was consistently negative for acid-fast organisms. The routine plate showed no significant changes. Bronchogram: A single fusiform dilatation of a bronchiole just above the diaphragm (figures 8 and 9).

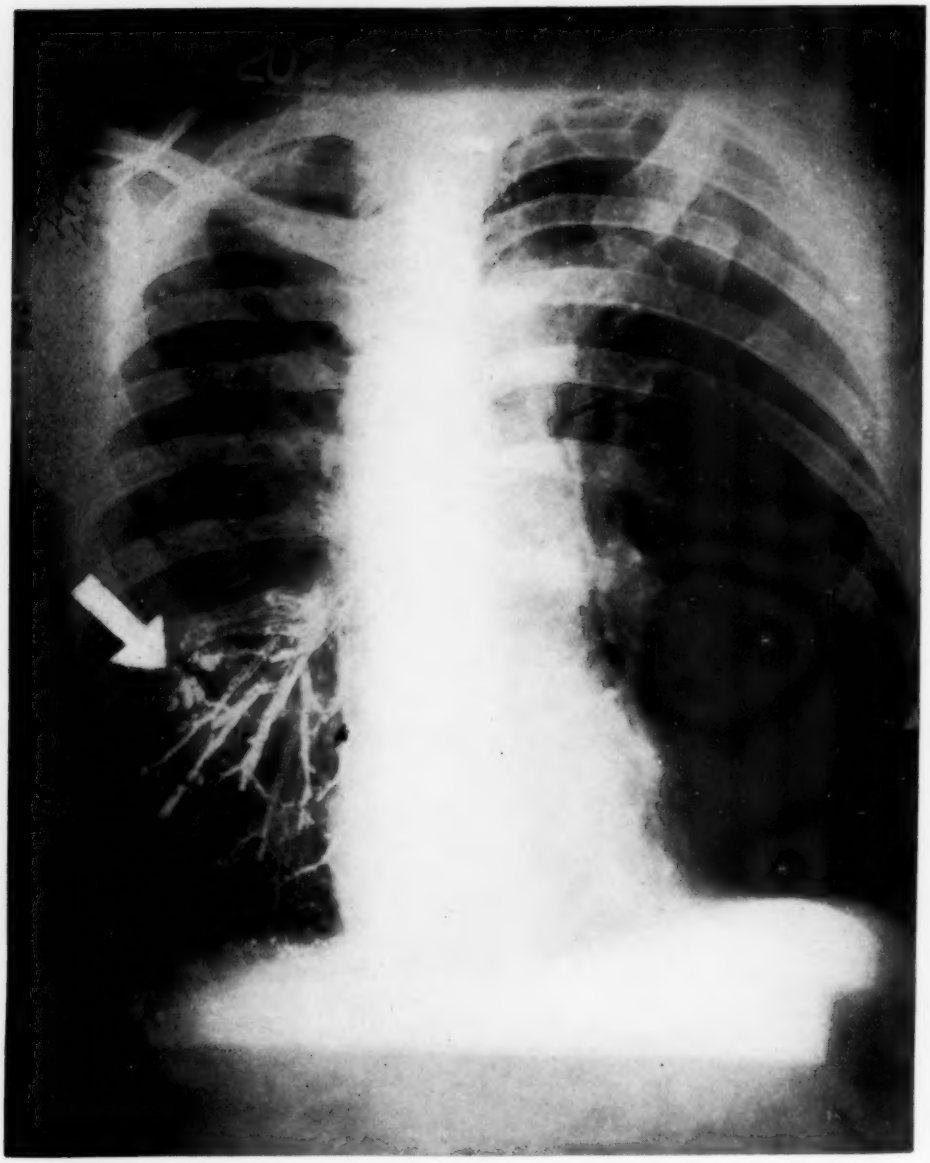

FIG. 7. D. D. W. Note sacculations in mid-lung field on left, residuals of an abscess.

As we have commented already, we feel that the last two cases must be regarded with suspicion. Case 7 is obviously an abscess residual and it is impossible to say whether the change represents a parenchymal pocket relined with bronchial epithelium (as we think likely) or a bronchial dilatation. Case 8 is presented largely for the fact that it apparently represents the most limited stage of disease, if we can call it disease. Certainly dilatation is

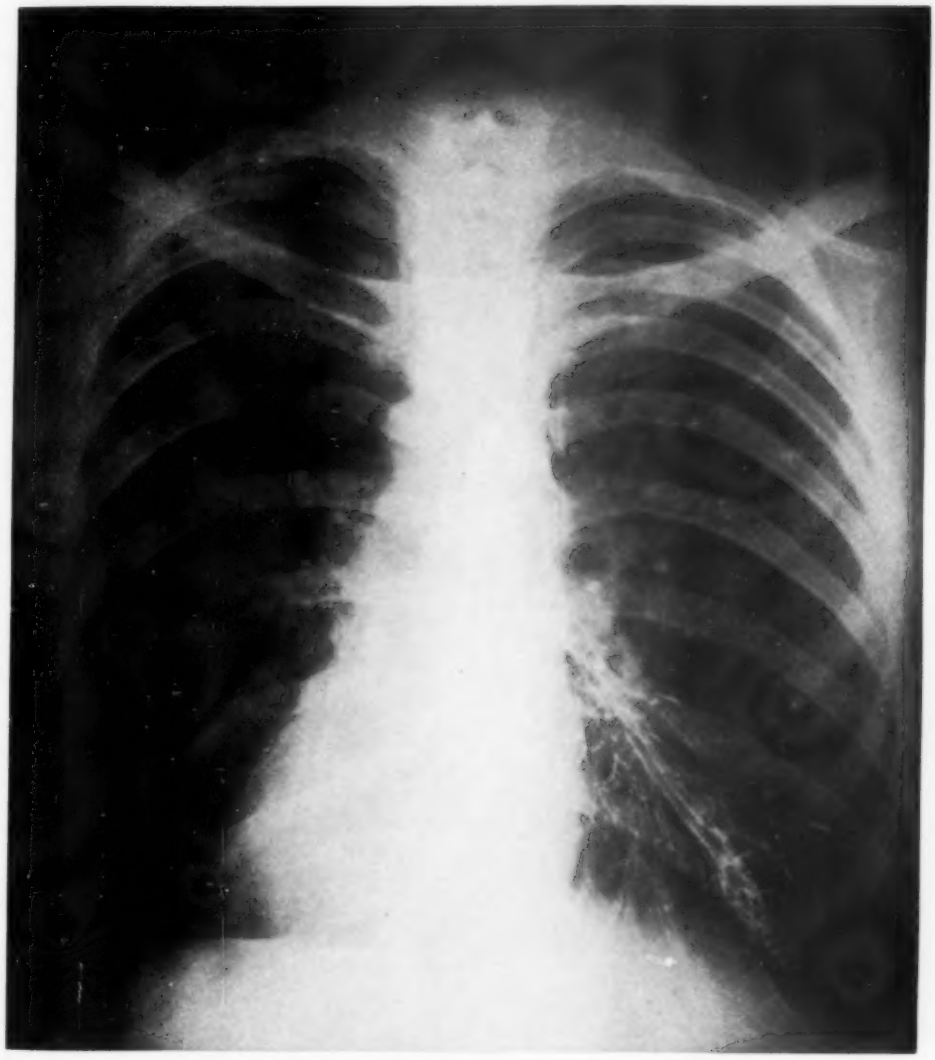

FIG. 8. C. D. A. A single dilatation just above the diaphragm.

present, but in spite of other reports having been negative we did not feel justified in giving the patient a diagnosis of non-tuberculous disease. Certainly we are unwilling to believe that so little dilatation was capable of causing his symptoms. We have seen in our files, however, two other cases in which a single bronchiole was definitely dilated. What their meaning may be we have not been able to determine.

Of the six cases of which we feel convinced, it is apparent that all presented some type of respiratory history, even though slight, and one or two had rather long histories. The sputum in general was but very slightly

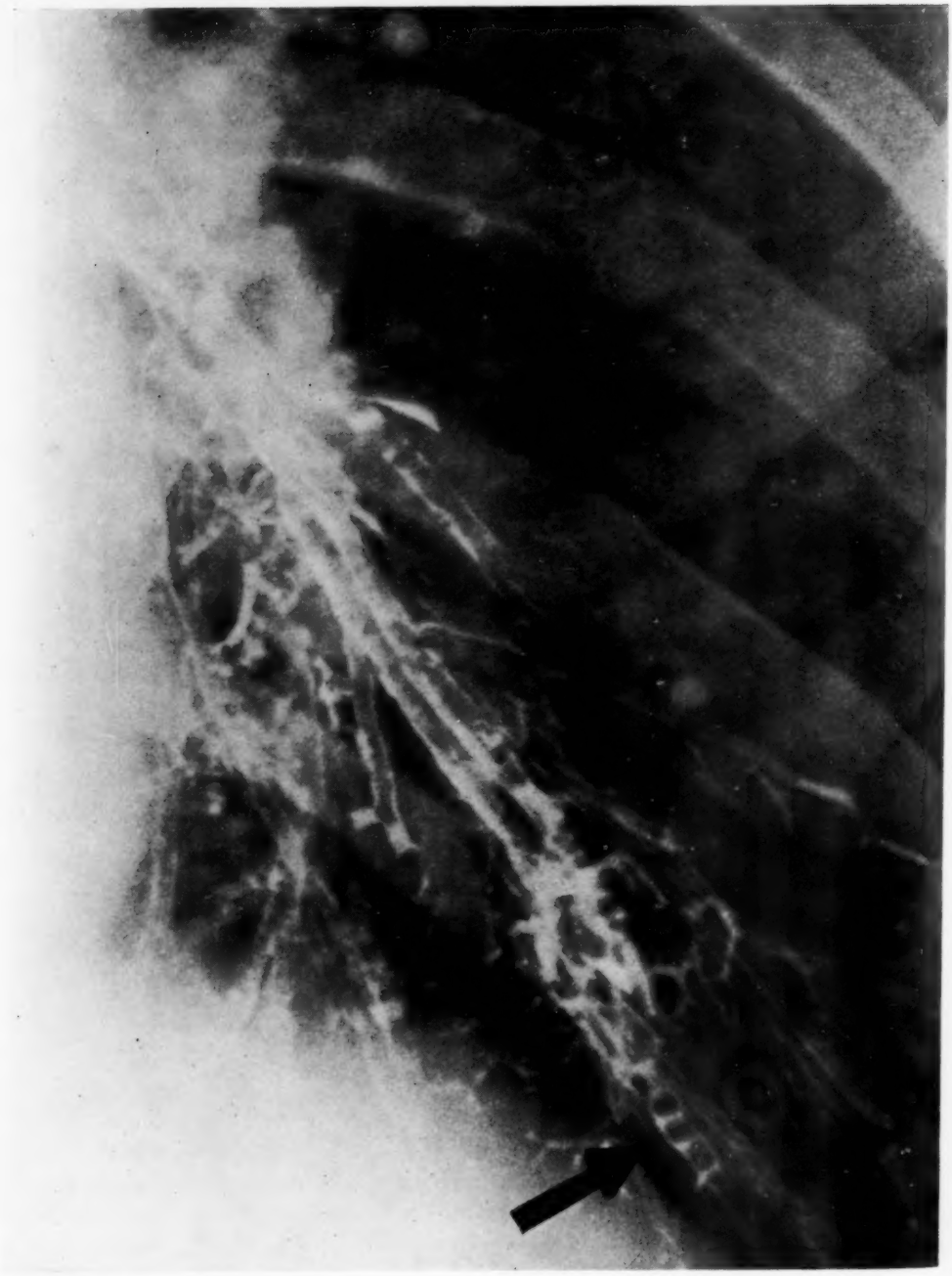

FIG. 9. C. D. A. Enlargement, approximately natural size from figure 8, shows detail of single dilatation. Compare with adjacent branches.

purulent, though one patient produced definite pus in small quantities. Hemorrhage was not prominent and when it occurred was rather slight. On the one hand, then, the symptoms were relatively mild, but on the other they were persistent and consistent.

The question that arises is whether or not there were other dilatations which we failed to find. Short of post mortem there can be no satisfactory answer. We made every effort to rule out such a possibility, but it always exists. We do not believe, however, that it is illogical to think that a few dilatations are capable of producing symptoms of the same type, though not of the same severity, as extensive bronchiectasis. Amberson is of the same opinion.[1] The same pathology that produces severe symptoms in an extensive lesion should be able to produce mild symptoms in a smaller one.

It is perhaps interesting to comment that all the cases which we consider acceptable show dilatations on the right side. Aside from the usual explanation that the right lower lobe has the straightest bronchial connection with the trachea we offer no suggestion as to the reason. Possibly it is nothing more than chance. In view of the fact that the dilatations in previously reported cases were all saccular, we call attention to the variety of types in our cases.

Conclusions

We present six cases of what we consider to be isolated or circumscribed bronchiectasis which is probably not as rare as the paucity of comment in literature might lead one to believe. It is believed possible that limited dilatation may produce the same quality but not the same degree of symptoms as more extensive disease.

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THE THERAPEUTIC EFFECTIVENESS AND POTENCY OF DIGILANID IN THE TREATMENT OF CONGESTIVE HEART FAILURE*

By ROBERT C. BATTERMAN, M.D., DELAVAN V. HOLMAN, M.D., and ARTHUR C. DEGRAFF, M.D., F.A.C.P., *New York, N. Y.*

OVER a period of years, evidence has been accumulating attesting to limitations of the bio-assay for digitalis bodies. Preparations of the same potency with regard to their ability to produce death in a cat or frog will vary markedly in their therapeutic potency as applied to man. Outstanding examples of this discrepancy are the purified digitalis glycosides, digitoxin, (Merck [1] or "digitaline nativelle" [2]) and Verodigen (Gitalin) [3, 4] and other members of the digitalis group such as g-strophanthin (Ouabain) [5] and Urginin.[6] This marked difference among various digitalis bodies has resulted in confusion. To substitute one preparation for another and still maintain the same level of therapeutic effectiveness requires the clinician to have extensive experience with and knowledge of each drug. It has led to the teaching that the clinician should familiarize himself with a single preparation and avoid the use of any other. Obviously the patient is deprived of the possibility of being treated with a preparation best suited for his individual needs. Furthermore, in our laboratory we have recently found that various samples of digitalis purpurea, although possessing identical cat unit potency, may be weaker or stronger as far as desired clinical therapeutic effects are concerned.

It is because of these limitations and objections to the accepted methods of bio-assay that it is desirable to obtain a digitalis body which can be standardized by gravimetric means. Such a preparation must maintain its potency over long periods of time. What is more important, it should consist of a definite and constant amount of a glycoside or proportion of glycosides which will always produce the same therapeutic effect in a given patient regardless of the sample dispensed.

Recently several digitalis bodies possessing the above qualifications have been introduced. It appeared desirable to study their therapeutic efficacy as compared with the whole leaf of digitalis purpurea. The present report deals with our observations with "Digilanid," † a mixture of constant proportions of three "pure" crystalline glycosides isolated by Stoll and Kreis [7] from digitalis lanata. None of the three glycosides, known respectively as lanatosides A, B and C singly satisfies the criteria for an ideal digitalis preparation.

* Received for publication October 28, 1940.

From the Department of Therapeutics, New York University College of Medicine and the Third (New York University) Medical Division of Bellevue Hospital.

† We are indebted to Sandoz Chemical Works, Inc. for the generous supply of material and other aid in connection with this investigation.

However, when combined with one another in proper proportions,† the result is a product of known chemical composition, which, according to the literature [8] compares favorably with the clinical effects of digitalis purpurea.

Selection of Material and Method of Study

The study was conducted on bed-ridden and ambulatory patients. Of the former a total of 30 patients was treated orally with digilanid. The final results, however, have been analyzed in only 23 of these, the remainder being excluded either because of insufficient data, administration of other medi-

Table I

Characteristics of Ward Patients Used in Study

Patient	Age	Sex	Diagnosis*			Degree† of Congestive Heart Failure	Weight‡ in Pounds
			Etiology	Anatomical	Physiological		
1	38	F	Hypertension	Enlarged heart, dilated aorta	RSR	++	227
2	65	F	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	165
3	53	M	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	147
4	56	M	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, dilated aorta	RSR	+	164
5	63	F	Rheumatic fever, hypertension	Enlarged heart, mitral insufficiency, mitral stenosis	AF	++	242
6	69	M	Arteriosclerosis	Enlarged heart, myocardial fibrosis	AF	+	134
7	43	M	Hypertension, syphilis	Enlarged heart, dilated aorta, aortitis, ostial stenosis	RSR	±	149
8	57	F	Hypertension, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	RSR	±	174
9	52	F	Rheumatic fever, hypertension	Enlarged heart, mitral insufficiency, mitral stenosis	AF	+	95
10	33	F	Hypertension	Enlarged heart	RSR	++	125 (ca)
11	63	M	Arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis	Auricular flutter	+	112
12	55	M	Hypertension, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	RSR	++	125

* According to criteria for diagnosis established by New York Heart Association.[10]

† Determined by general appearance of patient and clinical response during a preliminary period of control.

‡ Before digitalization.

† According to Sandoz Chemical Works, Inc. lanatosides A, B and C are combined in the approximate ratio of 47 : 16 : 37 respectively.

TABLE I—*Continued*

Patient	Age	Sex	Diagnosis*			Degree† of Congestive Heart Failure	Weight‡ in Pounds
			Etiology	Anatomical	Physiological		
13	64	M	Syphilis, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta, aortic insufficiency	RSR	++	138
14	66	M	Arteriosclerosis, unknown	Enlarged heart, coronary sclerosis, myocardial fibrosis	RSR	±	81
15	30	M	Rheumatic fever (active)	Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency, aortic stenosis	AF	+	128
16	58	M	Arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis	RSR	++	132
17	42	M	Rheumatic fever	Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency, aortic stenosis	RSR	+	149
18	69	M	Arteriosclerosis, hypertension	Enlarged heart, coronary sclerosis, myocardial fibrosis	RSR	+	178
19	60	M	Unknown (arteriosclerosis)	Undiagnosed	AF	N	117
20	62	M	Arteriosclerosis, unknown	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	AF	+	119
21	48	F	Unknown (rheumatic type)	Enlarged heart, mitral stenosis, mitral insufficiency	AF	+	166
22	61	F	Hypertension	Enlarged heart	AF	++	237
23	49	F	Hypertension, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	RSR	+	176

cation which would interfere with interpretation of results, or because they did not satisfy the criteria used for selection of patients for study. These criteria have been reported in detail elsewhere,[9] but the main points are worthy of repetition. The etiological diagnosis of the cardiac condition satisfied the criteria established by the New York Heart Association.[10] Patients with complicating conditions such as recent myocardial infarction, bronchopneumonia, chronic diffuse glomerulonephritis or fever of unknown origin were excluded. During the period of hospitalization, the patient must have exhibited some degree of congestive heart failure, although its presence may have been no longer discernible at the time of digitalization. Thus, patients with paroxysmal arrhythmias, but without congestive heart failure have been excluded. Finally, the patient must have been coöperative and capable of taking medication by mouth. This eliminated patients moribund

or too ill to offer a chance for a fair period of observation. Furthermore, none of the patients had received any digitalis preparation three weeks prior to hospitalization. The characteristics of the patients treated on the wards are summarized in table 1.

Following a preliminary control period in which the maximum effect of absolute bed rest, oxygen (if necessary), sedation, limited fluids and dietary restrictions was ascertained, the patient was digitalized rapidly with digilanid orally by one of two plans. The greatest number of patients (18) received within the first 24 hours approximately 0.1 cat unit per pound of body weight (equivalent to approximately 0.033 mg. of digilanid * (table 2) according to the method of Eggleston.[1] The patient was thereafter given large single daily doses equivalent to one half this amount until minor signs of toxicity were evident. The second plan, consisting of single daily doses of approximately 0.05 cat unit per pound of body weight until toxic effects were apparent, was used in five patients (table 3).

At least one electrocardiogram was taken before digitalization and at frequent intervals thereafter, usually daily, until evidence of toxic effects appeared. All patients were weighed daily, since as has been emphasized on several occasions,[9, 11] the weight curve is the best guide available at present for following the course of the patient's illness and is of particular help in patients with regular sinus rhythm where the diuresis reflected in the weight loss is indicative of a therapeutic effect. All patients were observed closely for evidences of improvement, changes in blood pressure, ventricular and pulse rates and symptoms and signs of toxicity.

In seven patients it was possible to compare the relative potency of digilanid and digitalis purpurea leaf under nearly identical conditions. All the patients received the digilanid first. After a suitable period, from 15 to 20 days, when the electrocardiogram had returned to normal form, digitalis purpurea leaf in tablets of 1 cat unit strength (equivalent to 0.1 gram) was given according to a dosage plan identical with that of the previously administered digilanid.

The suitability of digilanid for maintenance dosage was studied in a group of 20 ambulatory patients with chronic auricular fibrillation. The same care was used in the selection of patients for this group as in the case of those on the ward. All the patients had been under observation for months or years prior to this study so that their maintenance requirement with digitalis purpurea leaf was fairly well known. Since one of the factors under observation was a change in the cardiac reserve it was essential that the patients included for study be free of congestive heart failure when satisfactorily maintained with digitalis. These patients, therefore, were relatively asymptomatic unless their digitalis was discontinued or decreased. Using the cat unit potency as a guide, digilanid was substituted for digitalis

* Each tablet of "digilanid" contains 1/3 mg. of the mixture of the glycosides, lanatosides A, B and C, and is equivalent to 1 cat unit.

TABLE II

Therapeutic and Toxic Doses by Rapid Digitalization with Digilanid

Patient	Weight [1] in Pounds	Dose First 24 Hours				Therapeutic Effect	Therapeutic Dose						Toxic Effect	Toxic Dose						Remarks
		Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound		Days Required	Weight [2] in Pounds	Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound		Days Required	Weight [3] in Pounds	Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound	
1	227	24	0.106	7.92	0.035	Diuresis. Loss of 7 pounds	1	220 (ca)	24	0.109	7.92	0.036	Anorexia, nausea, vomiting, PR interval 0.28 second.	1	220 (ca)	24	0.109	7.92	0.036	Therapeutic effect overshadowed by toxicity.
2	165	16	0.097	5.28	0.032	VR slowing. Decreased dyspnea	1	165 (ca)	16	0.097	5.28	0.032	Nausea, vomiting, idioventricular tachycardia.	2	165 (ca)	23	0.139	7.59	0.046	Patient expired third day after digitalization.
6	134	15	0.112	4.95	0.037	VR slowing	1	134	15	0.112	4.95	0.037	Nausea, vomiting, diarrhea.	4	135	33	0.224	10.89	0.070	
7	149	16	0.107	5.28	0 035								Nausea, vomiting	7 *	145	51	0.351	16.83	0.115	Therapeutic effect indefinite. Minimal failure.
8	174	17	0.097	5.61	0.032								Nausea, vomiting, diarrhea.	2	174	27	0.156	8.91	0.052	Therapeutic effect indefinite. Minimal failure.
9	95	10	0.105	3.30	0.034	VR slowing	1	95	10	0.105	3.30	0.034	Nausea, vomiting, marked VR slowing.	3	95	19	0.200	6.27	0.066	
11	112	15	0.134	4.95	0.044	VR slowing. Diuresis	2	112	21	0.187	6.93	0.062	Nausea, vomiting.	5	106	39	0.367	12.87	0.121	Diuresis occurred concomitant with toxic dose. Loss of 6 pounds.
12	125	14	0.112	4.62	0.037								Anorexia, nausea, A-V nodal rhythm, transient complete A-V block.	2	124	20	0.161	6.60	0.053	Therapeutic effect overshadowed by toxicity.

[1] Weight prior to digitalization.
[2] Weight at time therapeutic effect was evident.
[3] Weight at time toxic effect was evident.
* Patient missed one dose on third day of digitalization.
† Excluding patient 15.

TABLE II—*Continued*

Patient	Weight [1] in Pounds	Dose First 24 Hours				Therapeutic Effect	Therapeutic Dose						Toxic Effect	Toxic Dose						Remarks
		Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound		Days Required	Weight [2] in Pounds	Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound		Days Required	Weight [2] in Pounds	Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound	
13	138	15	0.108	4.95	0.036	Diuresis. Loss of 6 pounds	2	132	22	0.166	7.26	0.55	Anorexia, nausea, vomiting.	4	127	36	0.283	11.88	0.093	Diuresis continued after digilanid was stopped. Weight loss of 14½ pounds in 7 days.
14	81	9	0.111	2.97	0.036								Anorexia, nausea, vomiting.	2	78	13	0.166	4.29	0.051	Therapeutic effect indefinite. Minimal failure. Overshadowed by toxicity.
15	128	14	0.109	4.62	0.036	VR slowing	4	122	32	0.262	10.56	0.086	Diarrhea, marked VR slowing.	22	116	140	1.2	46.20	0.378	6 cat units per day for 21 days before toxicity occurred.
17	149	16	0.107	5.28	0.035	Diuresis. Loss of 5 pounds	2	144	22	0.152	7.26	0.050	Multiple VPC's with coupling.	5	137	40	0.291	13.20	0.096	Total weight loss—13 pounds in 9 days.
18	178	20	0.112	6.60	0.037								Anorexia, nausea, diarrhea, visual disturbance, headache, prolonged PR interval to 0.25 sec.	2	176	24	0.138	7.92	0.045	Therapeutic effect indefinite. Minimal failure. Overshadowed by toxicity.
19	117	13	0.111	4.29	0.036	VR slowing	2	117	19	0.161	6.27	0.053	Marked VR slowing.	3	118	25	0.211	8.25	0.069	
20	119	13	0.109	4.29	0.035								Nausea, vomiting.	7	119	49	0.404	16.17	0.135	Therapeutic effect indefinite.
21	166	12	0.072	3.96	0.023	VR slowing. Diuresis. Loss 3 lbs.	2	162	18	0.111	5.94	0.036	Nausea, vomiting.	3	162	28	0.172	9.24	0.057	
22	237	26	0.109	8.58	0.036	Diuresis. VR slowing	1	230 (ca)	26	0.113	8.58	0.037	Anorexia, nausea, vomiting, visual disturbance.	2	230 (ca)	36	0.156	11.88	0.051	
23	176	19	0.107	6.27	0.035	Diuresis. Loss of 5 pounds	2	171	27	0.157	8.91	0.052	Anorexia, nausea, vomiting, diarrhea, prolonged PR interval to 0.25 sec.	2	171	27	0.157	8.91	0.052	
Average †									20	0.133	6.60	0.044				30.2	0.214	10.03	0.071	

TABLE III

Therapeutic and Toxic Doses by Second Plan of Digitalization

Patient	Weight[1] in Pounds	Dose First 24 Hours				Therapeutic Effect	Therapeutic Dose						Toxic Effect	Toxic Dose						Remarks
		Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound		Days Required	Weight[2] in Pounds	Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound		Days Required	Weight[3] in Pounds	Tablets or Cat Units	Cat Units per Pound	Mg.	Mg. per Pound	
3	147	7	0.047	2.31	0.015	Diuresis. Loss of 4 pounds. VR slowing	2	143	14	0.098	4.62	0.032	Nausea, vomiting. Abdominal cramps. Multiple VPC's	3	143	21	0.147	6.93	0.048	
4	164	7	0.042	2.31	0.014	Diuresis. Loss of 3 pounds	3	162	21	0.129	6.93	0.042	Nausea, vomiting. Anorexia	5	158	35	0.221	11.55	0.073	Total weight loss, 10 pounds in 8 days.
5	242	11	0.049	3.63	0.015	VR slowing. Diuresis. Loss of 4 pounds	2	242	22	0.090	7.26	0.030	Marked VR slowing. Anorexia. Nausea, vomiting	3	238	33	0.138	10.89	0.045	Total weight loss, 14 pounds in 12 days.
10	125 (ca)	6	0.048	1.98	0.015	Diuresis	2	125 (ca)	12	0.096	3.96	0.032	Nausea, vomiting	3	125 (ca)	18	0.144	5.94	0.047	Patient weighed with difficulty.
16	132	6	0.015	1.98	0.015	Diuresis. Loss of 6 pounds	4	126	24	0.190	7.92	0.062	Nausea. Visual disturbance. Multiple VPC's with coupling. Prolonged PR interval, 0.25 sec.	4	126	24	0.190	7.92	0.062	
Average									18.6	0.121	6.14	0.039				26.2	0.168	8.65	0.055	

[1] Weight prior to digitalization.
[2] Weight at time therapeutic effect was evident.
[3] Weight at time toxic effect was evident.

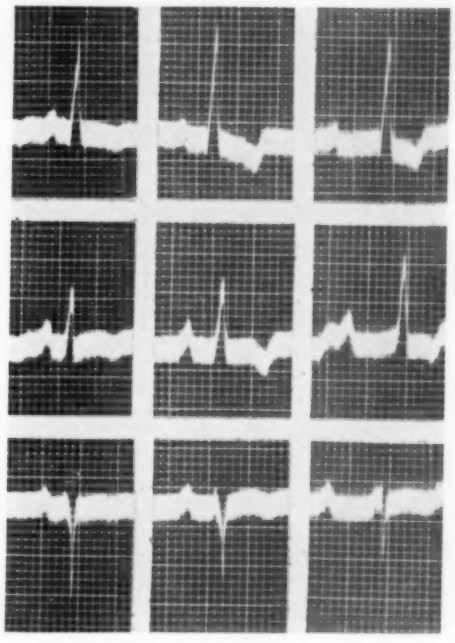

FIG. 1.

FIG. 1. Alterations in electrocardiographic complexes produced by digitalization with digilanid orally.

Patient 1: Hypertensive heart disease with enlarged heart and dilated aorta. (A) control, (B) after 24 cat units (7.92 mg.) in 24 hours, (C) 48 hours after digitalization. Digilanid discontinued after 24 cat units. Patient had marked diuresis with loss of 18 pounds of edema fluid.

leaf in identical doses. At each clinic visit, the patients were observed for alterations in the ventricular rate and development of objective signs of diminution in cardiac reserve. Particular attention was paid to gain in weight (especially if latent edema was suspected), to demonstrable edema of the extremities, moist râles of the lungs and liver enlargement.

RESULTS

The essential data obtained from the use of digilanid in 23 ward patients are summarized in tables 2 and 3. The number of mg. or cat units per pound constituting the therapeutic and the toxic doses of the drug was determined on a basis of the ratio of amount of drug to the weight of the individual at the time the desired effects were discernible. Since patients with edema are continually changing their bodily digitalis concentration as a result of diuresis, it is conceivable that such figures furnish more accurate data than if a single weight be used.

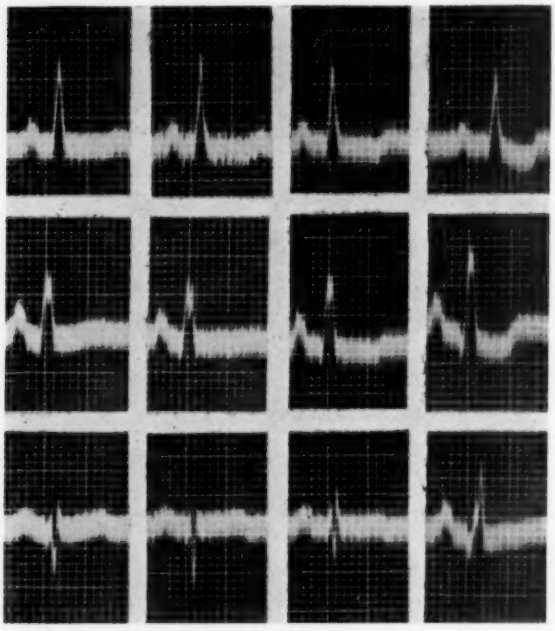

FIG. 2.

Patient 4: Hypertensive and arteriosclerotic heart disease with enlarged heart, myocardial fibrosis and dilated aorta. (A) control, (B) after 7 cat units (2.31 mg.), (C) after 14 cat units (4.62 mg.), (D) after 35 cat units (11.55 mg.). Associated with anorexia, nausea and vomiting.

With the exception of patient 15, a satisfactory therapeutic response was obtained in the group (table 2) digitalized rapidly by the method of Eggleston within one to two days with a dose ranging from 3.30 to 8.91 mg. (average 6.6 mg.) equivalent to 10 to 27 tablets or cat units (average 20 cat units) of digilanid. In six patients the therapeutic effect was indefinite either because of the minimal degree of congestive heart failure or because it was overshadowed by toxic manifestations. In three patients the therapeutic and toxic doses were apparently identical, perhaps due to the rapidity of digitalization. The toxic dose, with the exception of patient 15, ranged between 13 and 51 cat units (average 30.2) equivalent to 4.29 and 16.83 mg. respectively (average 10.03 mg.). Patient 15, a subject with active rheumatic heart disease, required 32 cat units (10.56 mg.) of digilanid over a period of four days before a therapeutic effect could be observed and 140 cat units (46.20 mg.) over a period of 22 days before toxic manifestations occurred.

Of the five patients who were digitalized according to the second plan of study (table 3), it is interesting to note that the therapeutic and toxic doses were within the range of the rapid method and that on the average,

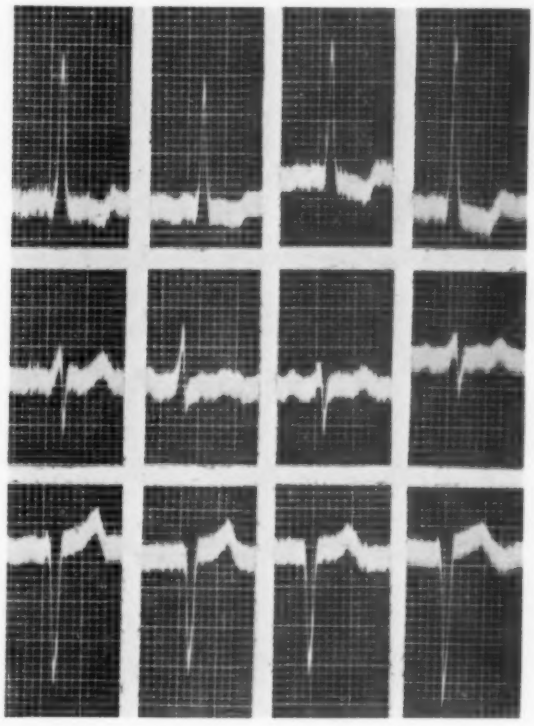

FIG. 3.

Patient 5: Rheumatic and hypertensive heart disease with enlarged heart, mitral stenosis and insufficiency. (A) control, (B) after 11 cat units (3.63 mg.), (C) after 22 cat units (7.26 mg.), (D) after 33 cat units (10.89 mg.). Associated with marked slowing of ventricular rate, anorexia, nausea and vomiting.

18.6 and 26.2 cat units respectively, they were surprisingly lower. Perhaps, if more cases with this method were available for analysis, this discrepancy would not have existed or may even have been reversed.

Comparative studies in seven patients are analyzed in table 4. Considering the impossibility of achieving exactly identical conditions it is striking that four patients (numbers 3, 6, 9, 11) required approximately the same amount of digilanid and digitalis purpurea leaf to produce similar therapeutic and toxic effects. The data on two patients (numbers 10 and 13) would indicate that digilanid was more potent than the leaf, while the opposite is true in the case of patient 4. When the average cat unit values of each preparation required for the therapeutic and toxic effects are compared, the similarity in potency is further emphasized.

Maintenance with digilanid was achieved without difficulty and in the same dose substituted for the digitalis leaf. Patients were observed for varying periods of time amounting in some instances to as long as 7 to 10

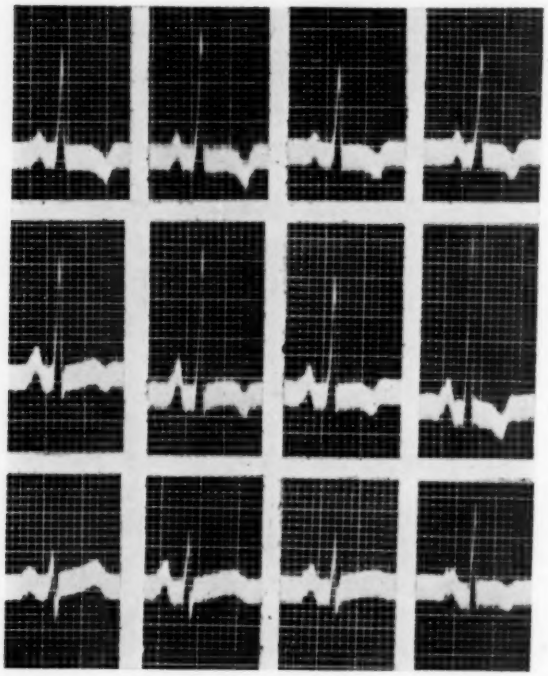

FIG. 4.

Patient 7: Hypertensive and syphilitic heart disease with enlarged heart, aortitis, dilated aorta and ostial stenosis (A) control, (B) after 16 cat units (5.28 mg.), (C) after 23 cat units (7.59 mg.), (D) after 37 cat units.

months. Objective evidence for superiority of one preparation over the other was lacking. An equal number of patients when taking digilanid were subjectively improved or claimed to be worse. However, when subsequent trials were given, the subjective effects were less apparent. In none of the cases were we certain of changes attributable beyond doubt to digilanid.

DISCUSSION

A digitalis preparation to be acceptable for routine clinical use must satisfy many criteria. When administered by mouth, it must be readily absorbable so that in the majority of cases a prescribed dose will produce, within limits of biological variation, a desired effect. The preparation, however, in addition to its ability to be absorbed, must be effective in increasing the cardiac reserve or do any other task required of digitalis. The preparation must be a potent one according to the accepted methods of standardization, although once its potency is thus established, it is desirable to be able to rely for dosage on gravimetric assay. Furthermore its potency must be such that the ratio of toxic to therapeutic dose; i.e., its

TABLE IV

Comparative Therapeutic and Toxic Doses of Patients Digitalized with Digilanid and Digitalis Purpurea Leaf

Patient	Digilanid								Interval Between Preparations in Days	Digitalis Purpurea Leaf								Remarks
	Therapeutic Dose				Toxic Dose					Therapeutic Dose				Toxic Dose				
	Weight[1] in Pounds	Cat Units	Cat Units per Pound	Days Required	Weight[2] in Pounds	Cat Units	Cat Units per Pound	Days Required		Weight[1] in Pounds	Cat Units	Cat Units per Pound	Days Required	Weight[2] in Pounds	Cat Units	Cat Units per Pound	Days Required	
3	143	14	0.098	2	143	21	0.147	3	19	148	14	0.094	2	148	28	0.188	4	
4	162	21	0.129	3	158	35	0.221	5	15	—	—	—	—	160	14	0.087	2	Therapeutic effect indefinite for digitalis leaf.
6	134	15	0.112	1	135	33	0.224	4	20	142	15	0.105	1	142	39	0.274	5	
9	95	10	0.105	1	95	19	0.200	3	19	96	20	0.208	3	92	25	0.271	4	
10	125 (ca)	12	0.096	2	125 (ca)	18	0.149	3	16	118	12	0.101	3	116	30	0.238	5	
11	112	21	0.187	2	106	39	0.367	5	18	111	21	0.189	2	109	39	0.357	5	
13	132	22	0.166	2	127	36	0.283	4	19	—	—	—	—	129	64	0.495	8	Therapeutic effect indefinite for digitalis leaf.
Average		16.4	0.128			28.7	0.227				16.4	0.139			34.1	0.272		

[1] Weight at time therapeutic effect was evident.
[2] Weight at time toxic effect was evident.

therapeutic range, be large. Cumulation and elimination of the drug must be at a rate compatible with the possibility of producing complete digitalization and subsequently maintaining this level satisfactorily. The preparation must be stable and the potency of various lots should not vary. Finally, it must be easy to administer and tolerated by the patient as far as local gastrointestinal irritation is concerned.

Digilanid is readily absorbable and its effectiveness as far as could be determined appears to be identical with powdered digitalis leaf. A satisfactory therapeutic response is obtained with both the bed-ridden and ambulatory patients. In the former diuresis and slowing of the ventricular rate, if the patient has auricular fibrillation occurred in the majority of patients within a reasonably short period of time. Furthermore, characteristic alterations of the electrocardiogram (figures 1 to 4) are produced with a dose comparable to that of digitalis.

The clinical potency of digilanid, cat unit for cat unit, appears to be identical with that of digitalis purpurea leaf. The average therapeutic dose of 20 cat units and toxic dose of 30 cat units are in close agreement with the generally accepted figures for the leaf. The similarity is further strengthened by the data obtained in the seven patients (see table 4) in whom both preparations were compared and in the ambulatory group where one preparation was substituted for the other. In the latter group, there were no consistent differences found in either the subjective or objective effects. In a few cases questions arose concerning subjective advantages or disadvantages, but in all instances, when tried a second time after an interval, the apparent difference was not repeated.

The ratio of toxic to therapeutic dose also appears to coincide with the general experience in the use of digitalis. Individual variations are to be expected, but with the exception of the three patients who became toxic too rapidly to determine the therapeutic dose and of patient 15, who had active rheumatic heart disease, the therapeutic effects occurred after administration of between 45 per cent and 76 per cent of the toxic dose.

It is not sufficient that a preparation produce digitalization when administered at repeated short intervals, but the rate of elimination and therefore its ability to accumulate must be such that slow digitalization and maintenance of a desired therapeutic effect is possible. Digilanid also satisfies this criterion. This is well illustrated in the group of five patients digitalized by our second plan of study and in the group receiving a maintenance dose within the limits set by clinical experience.

No difficulty was experienced with regard to the administration of the preparation. Although gastrointestinal irritation was to be expected with any drug taken by mouth this was not observed in the 43 patients studied. This in itself may be a minor advantage of digilanid over digitalis leaf, but the number of cases reported is not sufficiently large to warrant this conclusion.

As pointed out in the introduction, one of the disadvantages in the use of digitalis leaf is the varying clinical potency in man although the different samples of leaf possess identical cat unit values. If the gravimetric method of assay permits greater accuracy and uniformity of dosage regardless of the sample dispensed, then digilanid would possess definite advantages over the powdered leaf of digitalis purpurea.

Experience with digilanid, therefore, permits one general conclusion. The mixture of pure crystalline glycosides combined in constant proportions satisfies with a high degree of perfection the criteria for a satisfactory digitalis preparation. The similarity of digilanid and digitalis leaf with regard to fundamental pharmacological and clinical properties is impressive. This is in close agreement with the recent report of Adams and Gregg.[12]

Summary

1. The therapeutic efficacy and potency of digilanid, a mixture of pure crystalline glycosides present in digitalis lanata, has been studied in 23 hospitalized and 20 ambulatory patients.

2. The therapeutic and toxic doses of digilanid in terms of cat unit potency were found to be identical with those of digitalis purpurea.

3. The similarity of digilanid and digitalis leaf with regard to fundamental pharmacological and clinical properties is discussed.

4. Digilanid satisfies the established criteria for a reliable potent digitalis preparation.

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THE FOLLICULAR TYPE OF MALIGNANT LYMPHOMA; A SURVEY OF 63 CASES *

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So-called follicular lymphoma was first identified by Brill, Baehr and Rosenthal in 1925.[2] They did not at this time consider it a neoplastic phenomenon and suggested the term giant follicle hyperplasia. Shortly afterward several similar cases were recorded by Symmers, who likewise assumed a non-neoplastic background.[8] The former authors ultimately revised their beliefs and at the present time consider the disease a form of lymphoblastoma.[1, 7] Symmers, however, has retained his original concept, although admitting frequent transition of the process into frank neoplasm.[9] Callender included this disease in the group of hematopoietic tumors [3] and Jackson has stated that the disorder frequently progresses into one of the other forms of malignant lymphoma.[5, 6]

The series which we report consists of 63 cases of follicular lymphoma, biopsy or necropsy material from which was submitted to the Laboratory of Pathology of the Massachusetts General Hospital during the period from 1917 to 1939. Fifty-nine had relatively complete clinical data and in 29 there was sufficient roentgenologic material for thorough analysis. Discussion has been divided into histologic, clinical, roentgenographic and therapeutic observations in order to demonstrate the identity of the disease.

Pathologic Observations

The striking fashion in which the histologic structure of follicular lymphoma differs from that observed in other types of malignant lymphoma probably accounts for the fact that its incorporation into this category is a comparatively recent event. In fact, the apparent resemblance to the structure of simple lymph node hyperplasia has caused several authorities to consider the disease merely a manifestation of chronic non-neoplastic irritation. There can be so little question, however, that the condition leads almost invariably to a lethal outcome and the clinical manifestations are so similar to those exhibited by other forms of lymphoma that we have not hesitated to consider it a histologic variant of this disease complex. Jackson [6] has stated that it represents an early form of malignant lymphoma and may become transformed into any of the other recognized types. Callender has frankly considered it to be a lymph node tumor and attributed to it a rapidly fatal course.

* Received for publication June 25, 1940.
From the Department of Pathology and Bacteriology, the Department of Roentgenology, and the Department of Medicine of the Massachusetts General Hospital, Boston.

In our material, follicular lymphoma has been manifested by moderate to enormous enlargement of lymph nodes with replacement of the normal architecture by multiple follicle-like nodules of varied size and approximation. Normal sinus structure was obscured and the capsule frequently encroached upon. Invasion of perinodal tissues was not common but when present, interestingly enough, exhibited follicle-like arrangement even beyond the confines of the lymph node (figure 3).

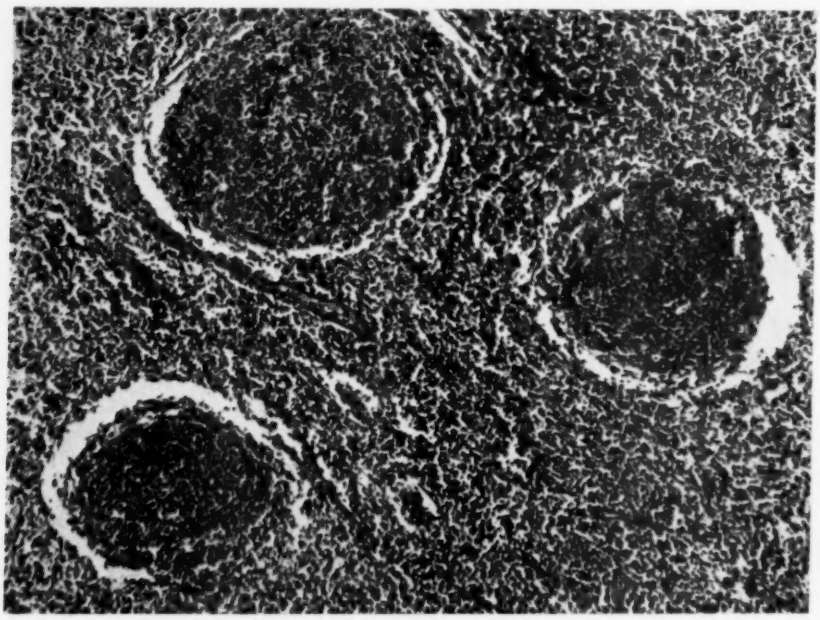

FIG. 1. Nodal structure intervening between follicles consists of a "matrix" of closely packed lymphoid elements obscuring the normal architecture. The follicles which are Type I in character exhibit the "cracking-off" phenomenon. × 150.

Review of the sections revealed two essentially fundamental structural variations. One consisted of closely packed, rounded or oval shaped, follicle-like nodules of inconstant size but similar intrinsic morphology (figure 2). The intervening tissue consisted only of thin strands of small lymphocytes or compressed reticular substance. The other type also consisted of innumerable widely distributed follicles exactly similar to those noted above. Instead of lying in immediate proximity to each other, however, they were separated by broad homogeneous masses of small lymphocytes (figure 1). The follicles seemed set, more or less, in a lymphocytic matrix which was otherwise characteristic of the so-called lymphocytic form of lymphosarcoma. In these the architecture of the node appeared to be more completely obliterated by the combined processes.

Silver stains for argentophilic fibrils revealed a characteristic revision of supportive structure; this in the reticulum framework of the lymph node. In

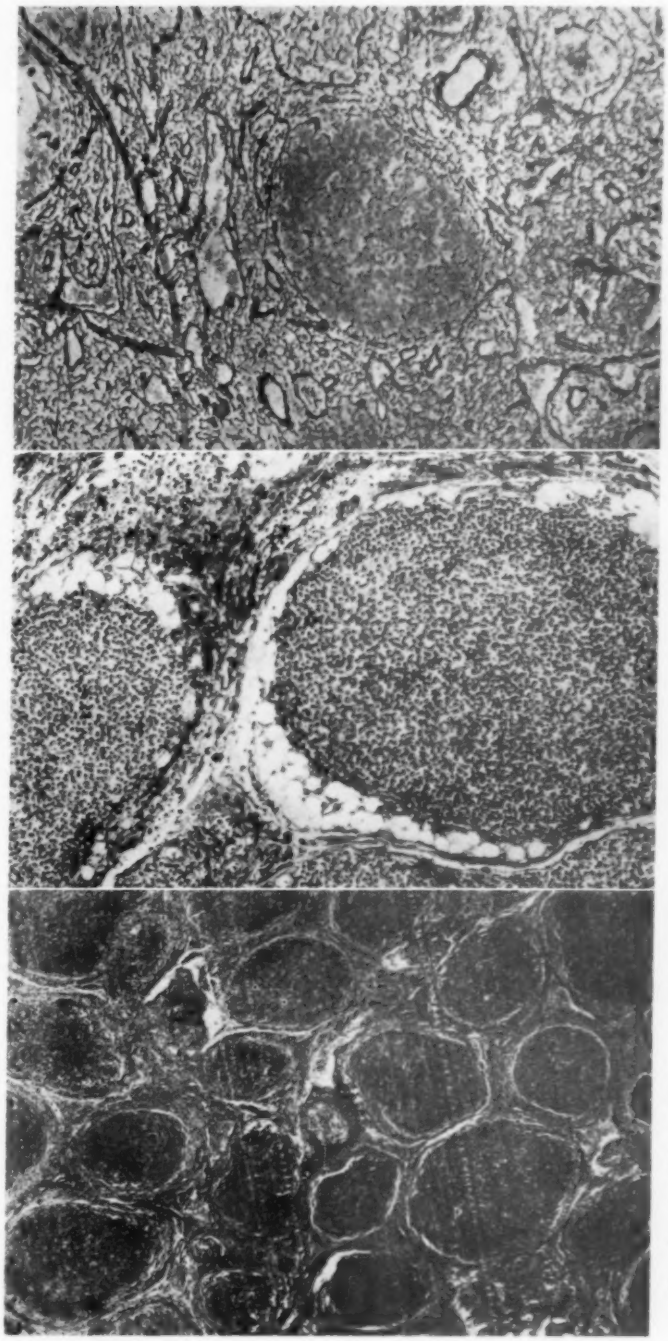

FIG. 2. (Left) Follicles are homogeneous in character (Type I). Intervening stroma is compressed, but normal landmarks persist. × 75.

FIG. 3. (Center) An example of extranodal invasion in which follicular arrangement is evident. The two follicles are encompassed by pericapsular fat. × 200.

FIG. 4. (Right) A silver stain demonstrating the reticulum structure of a normal lymph node. × 200.

normal lymph nodes this procedure demonstrated no staining of the collagen fibers composing the capsule and major trabeculae. Extending from these, however, was a loose, fairly regular meshwork of fine argentophilic reticulum fibrils (figure 4). At the edges of the sinuses and follicles the reticulum showed abrupt transition to a relatively sparse, irregular, noninterlacing prolongation of fibrils.

In follicular lymphoma a distinct revision of fibrillar elements appeared. The reticulum meshwork surrounding each nodule was distorted and condensed by follicular expansion (figure 5). The normal loose network with

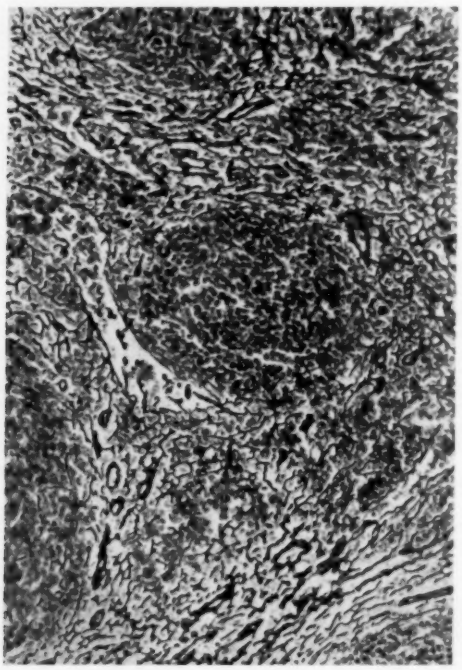

FIG. 5. A silver stain of follicular lymphoma. The compressed character of the reticulum fibrils with absence of collagenization may be observed. × 200.

broad polygonal pulp spaces became compressed and the interreticular crevices were elongated and narrowed. The disappearance of the sinuses appeared to be the result of the displacement of reticular substance and pulp content. Despite the condensation of fibrils, fusion and collagen formation did not occur. All other types of lymphoma produced destruction of reticulum with the reappearance in some of scanty disconnected fibrils and in others of a fibrous stroma with no resemblance at all to the normal architecture. Ordinary hyperplasia caused no significant reticular rearrangement. This feature was, therefore, of considerable morphologic diagnostic value.

The compactness of the reticulum at the periphery of each of the nodules caused the transition into the follicles to become even more abrupt than usual.

Such fibrils as were observed extending into the follicles were few, irregularly arranged, frayed, and stunted in appearance. These sparse, stretched attachments to the surrounding framework were often ruptured in the course of fixation and sectioning, and permitted separation of the follicles from the encompassing stroma. "Cracking off" of nodules was admittedly an artefact but it was sufficiently peculiar to follicular lymphoma and so relatively inconspicuous in nonspecific hyperplasia that it was believed to offer a degree of differential diagnostic assistance (figures 1 and 2).

Sections stained in the routine manner with phloxine and methylene blue after fixation in Zenker's fluid were studied for the purpose of distinguishing

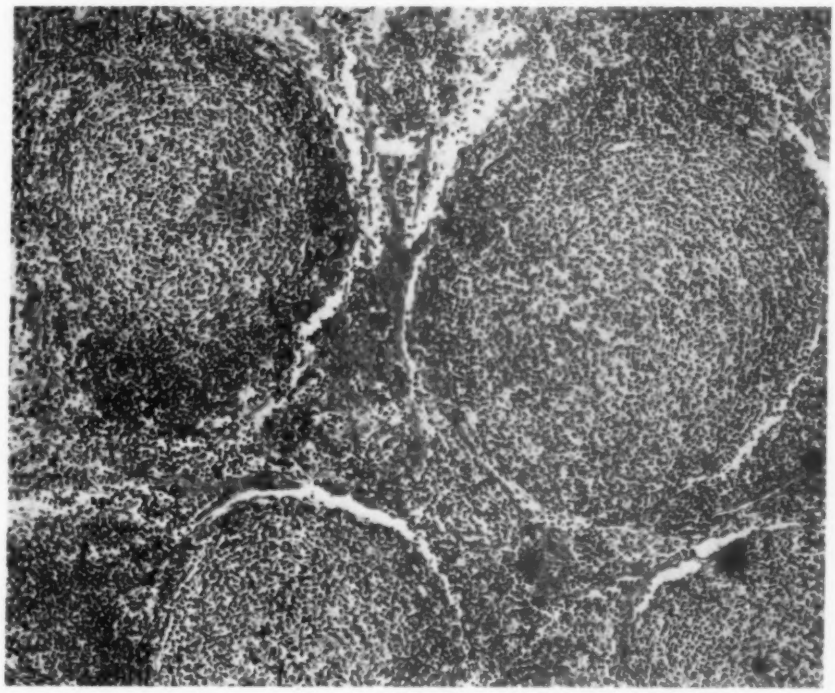

FIG. 6. An illustration of Type II follicles with well defined germinal centers. × 200.

fine cytologic variations. The dual character of the pulp intervening between nodules has been discussed above. Follicular components when subjected to detailed examination were found to exhibit a more marked variation than was originally suspected. Transition forms of all sorts were noted from nodules with relatively simple structure to those which were sufficiently complicated to offer difficulty in recognizing the basic follicular background. Despite a wide degree of morphologic overlapping, however, the follicular nodules were found to be susceptible to division into four major forms, arbitrarily termed Types I to IV.

The simplest of these, Type I consisted of homogeneous nodules comprised uniformly of small lymphocytes without germinal center formation or

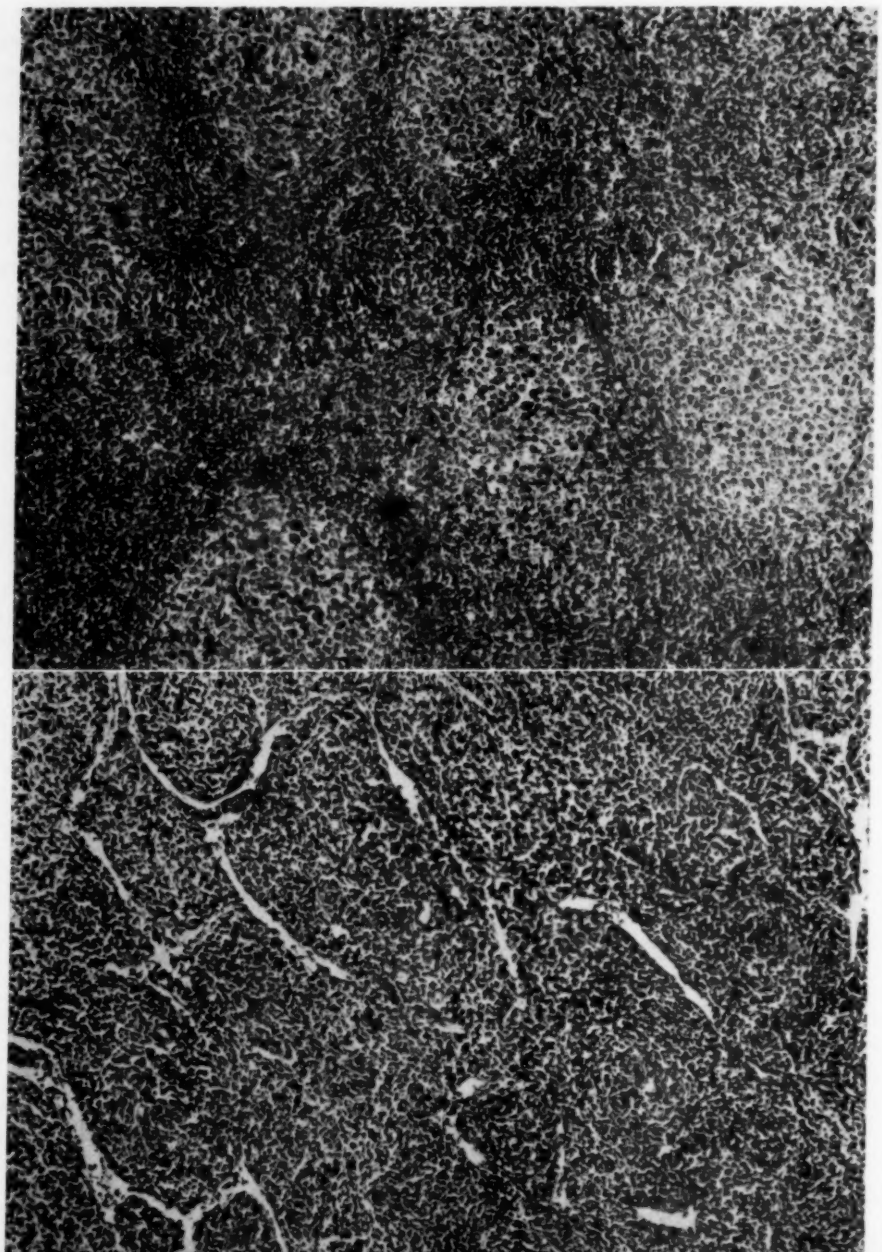

FIG. 7. (Above) Type III follicles with loss of peripheral rims of small lymphocytes. The follicles consist wholly of loosely arranged, polymorphous, germinal center elements. × 200.

FIG. 8. (Below) The interlacing strand-like arrangement of the follicles in the Type IV lesion. There is fusion of many nodules composed wholly of polymorphous elements but the follicular background is still perceptible. × 200.

significant intermixture with less mature elements (figures 1 and 2). Follicles classified as Type II showed slight to marked germinal center formation (figure 6). The central contents of these consisted of pale staining, compactly and occasionally concentrically arranged cells, the nature of which was difficult to determine with unequivocal accuracy. Some appeared to be primitive stem cells with large, round, vesicular nuclei, prominent nucleoli with scanty radially arranged chromatin, and ill defined, inconstantly staining cytoplasm. Other cells, approximately 10 to 15 microns in diameter, possessed a well delimited, abundant eosinophilic cytoplasm, and dark staining, irregular, reniform nuclei. These occasionally exhibited a phagocytic character and were not unlike clasmatocytes in appearance. Mingled with these elements were a few lymphoblast- and lymphocyte-like cells and moderate numbers of mitotic figures. Surrounding the germinal center and varying in thickness inversely with the size of the center, was a rim of wholly mature lymphocytes. The nodules were all uniformly round or oval in shape although there was considerable variation in diameter.

Three essential modifications distinguished the Type III lesion. The follicular rim of lymphocytes was lost and the entire nodule was made up of germinal center elements (figure 7). Among these the phagocyte-like cells predominated but many had assumed bizarre form and anaplastic qualities. Nuclei were larger, somewhat more vesicular, and there were increased numbers of mitotic figures. The cells were not unlike those observed in reticulum cell sarcoma. Both these and the stem cells occasionally exhibited incomplete division with the development of multinucleated cells resembling but not quite identical with those characteristic of Hodgkin's lymphoma. Finally, there was loss of the compact appearance observed in the Type II follicles and instead, a loose edematous structure, the cells of which were separated by clear spaces of varying magnitude in which were found dark staining fragments of apparent nuclear debris. The follicles were somewhat larger than those observed in the preceding types and showed minor variation in configuration manifested by short pseudopod-like projections. Sharp distinction from pulp elements persisted, but the occasional fusion of two or more impinging follicles occurred, with confluence of their contents.

Extensive deformity of the follicles led to the establishment of what has been termed the Type IV lesion. These follicles were quite large, completely irregular, and appeared as interlacing strands of elements entirely similar in cytologic character to those described above. Further atypicality and dedifferentiation were apparent but in no instance was there complete fusion with total replacement and obliteration of structure as was the case in other forms of lymphoma (figure 8). Nodules did appear to rupture occasionally, and in a patchy fashion intermixture of follicular and pulp cells was noted. In several cases follicular irregularity with large sweeping strands often extending through several low power fields presented so unusual an

appearance that identification as follicular lymphoma was difficult. A high degree of polycellularity and the occasional appearance of giant cells simulated Hodgkin's disease but the persistence in part of some follicular structure served to differentiate the lesion. Silver stains offered further differential assistance in this regard, for these demonstrated the persistence and compression of extrafollicular fibrils. Scirrhous Hodgkin's lymphoma, it is true, may exhibit nodular aggregation of neoplastic elements separated from each other by strands of collagenous fibers but despite marked compression of reticulum in the true follicular disease no significant collagenization ever appeared.

These observations of morphologic variation suggest a recognizable histogenic pattern. The four types described represented fairly distinct histologic entities and there was a sufficient degree of overlapping to permit the assumption that each was a different phase of the same basic process. In an attempt to seek clinical confirmation, 41 cases were analyzed with this thesis in view. These were found to be roughly equally divided among the four histologic follicular types. By breaking down the total duration of illness in these cases into the period preceding and that following biopsy it became evident (table 1) that the duration of symptoms before biopsy was

TABLE I

Follicular Lymphoma Type	Duration of Symptoms Preceding Biopsy	Duration of Disease After Biopsy	Total Duration
I	2.0 years	5.7 years	7.7 years
II	3.6 years	3.2 years	6.8 years
III	4.1 years	1.8 years	5.9 years
IV	4.1 years	2.3 years	6.4 years

shortest for Type I lesions, intermediary for Type II, and longest for Types III and IV. The duration of disease subsequent to biopsy, as had been suspected, was longest among the Type I cases and roughly progressively shorter for the remaining types. The total average duration for each group, although not entirely similar, bore a closer relationship to each other than to the other forms of lymphoma. These figures were not altogether conclusive but they did offer a reasonable degree of evidence that the histologic lesions described could represent progressive phases in the development of follicular disease.

Jackson [5, 6] has suggested that ultimate follicular fusion would produce lesions similar to those of the other types of lymphoma. In eight cases of our follicular series second biopsies (6) or necropsies (2) were made at intervals of two to eleven years after the initial biopsy. The average interval was about six years. Table 2 records the morphologic changes which were encountered and the intervals between the specimens studied.

Five of the eight cases showed changes consistent with the progression of the follicular lesion from an earlier to a later stage. Case III, in whom

no evidence of lymphoma was found at necropsy following death from an unrelated disease, had been subjected four and a half years earlier to a radical surgical excision of a lymphomatous mass in the groin. Since no recurrence occurred this must be considered one of the rare cases in which surgical cure was achieved. Case IV at autopsy showed persistence of a Type IV lesion six and a half years after the original biopsy was obtained. This patient succumbed to massive hemorrhage following irradiation of an epidermoid carcinoma of the cervix. Two other cases not shown in table 2 were autopsied. One died at another institution and was said to have shown generalized lymphoma. We have not had the opportunity of reëxamining these

TABLE II

Variation in Histologic Structure

Case	Nature of Material	Interval between Specimens	Type of Lesion	Remarks
I	Lymph node Lymph node	10 years	Type I Type II	Died with lymphoma
II	Lymph node Lymph node	11 years	Type I Type III	Alive with lymphoma
III	Lymph node Autopsy	4.5 years	Type I None	Died, unrelated disease
IV	Lymph node Autopsy	6.5 years	Type IV Type IV	Died, unrelated disease
V	Lymph node Epidural tumor	2 years	Type II Lymphoblastic lymphoma	Died with lymphoma
VI	Lymph node Lymph node	7 years	Type II Type IV	Alive with lymphoma
VII	Lymph node Lymph node	2 years	Type II Type IV	Died with lymphoma
VIII	Lymph node Lymph node	5.5 years	Type II Type IV	Died with lymphoma

tissues. The other patient died as the result of prostatism and was found to have Type I follicular lymphoma in many retroperitoneal nodes, a condition entirely unsuspected clinically. In case 5 alone was there evidence that the theory advanced by Jackson might be correct. In this case no postmortem examination was done, but an extranodal recurrence with the histologic appearance of lymphoblastic lymphoma (lymphosarcoma) appeared two years after an original biopsy showed Type II follicular disease. In spite of this one case, however, at least five of the remaining cases very definitely indicated a progression from simpler to more complex follicular structure as a natural feature of the lesion. The contention that the follicular variations described above probably do represent stages in the pathogenesis of the lesion was adequately supported.

Symmers has described four structural modifications which may occur in follicular lymphoma.[9] One of these he has termed "polymorphous cell sarcoma," a second was indistinguishable from Hodgkin's disease, a third ultimately developed lymphatic leukemia, and a fourth showed focal follicular necrosis. We have not had occasion to observe the latter type of lesion in any of our specimens but we have seen very similar processes in lymph nodes of patients with acute disseminated lupus erythematosus and Taussig [10] has described somewhat similar lesions in otherwise normal lymph nodes subjected to irradiation. "Polymorphous cell sarcoma" is apparently similar by description and illustration to those changes we have considered representative of advanced (Types III and IV) follicular lymphoma. We are in agreement with Symmers that this represents an end phase of the disease but it is not our opinion that it constitutes a different disease. Several of the Type III and IV lymph nodes, particularly the latter, have exhibited cellular pleomorphism and multinucleated cells simulating the appearance of Hodgkin's disease. In these, however, it has been felt that the presence of follicular residua, the characteristic compression of reticulum, the absence of true fibrosis, eosinophiles, plasma cells, and the dissimilarity of the multinucleated elements from typical Sternberg cells have all obviated a diagnosis of true Hodgkin's disease. None of our cases developed lymphatic leukemia.*

Clinical Observations

Records of 507 cases of malignant lymphoma exclusive of the follicular type were consulted for purposes of clinical contrast. Histologic preparations from all of these had been studied and classified variously as Hodgkin's lymphoma (174 cases), Hodgkin's sarcoma (33 cases), lymphocytic lymphoma (118 cases), lymphoblastic lymphoma (76 cases), stem cell lymphoma (42 cases), and reticulum cell sarcoma (64 cases).† Table 3 contrasts the clinical features exhibited by follicular lymphoma with those of the remainder of the malignant lymphomas. The latter were analyzed together without consideration of structural variation, although it was appreciated that the different subtypes varied significantly from one another in many features. Our purpose in ignoring these facts arises from the basic intention of establishing the identity of follicular lymphoma from lymphoma in general.

The great majority of the cases studied were dead and therefore complete information was available. Among the 63 cases of follicular disease, however, only 32 were known to be dead (3 dying of unrelated ailments), 17 were alive and under observation, and 14 were listed as lost although follow-up periods up to five years were recorded.

* Since the submission of this report we have encountered a case of follicular lymphoma with the peripheral blood picture of lymphocytic leukemia.

† The terminology cited represents a nomenclature established on the basis of morphologic criteria as the result of an extensive study of 617 cases of malignant lymphoma. The results of this survey will be published elsewhere by Dr. Tracy B. Mallory and one of us (E. A. G.).

The age of onset, computed on the basis of the earliest symptom attributable to lymphoma, was considerably later with the follicular process. Although the average age of 50 years was also the mean age, 43 per cent occurred between 30 and 50 years and only 7 per cent under the age of thirty. The younger age of initiation of symptoms among the lymphomas (41.7 years) was characterized by a wider distribution throughout all decades. It is thus somewhat unreasonable to consider the follicular lesion an early process from which other forms of malignant lymphoma arise inasmuch as it appears at a considerably later age than the other types of lymphoma.

TABLE III

	Follicular Lymphoma	Malignant Lymphoma (Exclusive of the Follicular Type)
Average age of onset	50.0 years	41.7 years
Onset under 20 years	3.5%	14.0%
Onset over 40 years	72.0%	54.0%
Average total duration	6.0 years	3.0 years
Mortality under 2 years	21.0%	56.0%
5 year survivals	47.0%	19.0%
10 year survivals	11.0%	4.0%
Sex (male : female)	1.2 : 1	2.4 : 1
Obstructive phenomena	46.0%	33.5%
Peripheral edema	28.0%	13.0%
Hydrothorax	21.0%	21.0%
Ascites	21.0%	17.0%
Fever	16.0%	42.0%
Peripheral lymph nodes	89.0%	85.0%
Retroperitoneal lymph nodes	63.0%	48.0%
Mediastinal lymph nodes	29.0%	46.0%
Splenomegaly	33.0%	40.0%
Gastrointestinal involvement	2.0%	14.0%
Genitourinary involvement	5.0%	10.0%
Pulmonary involvement	2.0%	9.0%
Cutaneous involvement	5.0%	21.0%
Discrete bone involvement	9.0%	14.0%
Anemia	18.0%	39.0%
Leukocytosis	7.0%	46.0%
Lymphocytosis	5.0%	34.0%
Atypical cells in blood	9.0%	29.0%
Leukemia	0	18.0%

Total duration was twice as long (6 years) in follicular lymphoma as in the other types (3 years). More than one half of the patients in the miscellaneous lymphoma group had expired during the first two years of their illness, whereas only one-fifth of those with follicular disease died within the same period. In fact, almost one half of these patients lived at least five years after onset, while a bare 19 per cent of the mixed cases survived this period. Of the 17 individuals alive with follicular lymphoma at the present time, the average duration is 6.8 years; those cases which had succumbed had lived 5.2 years.

The proportion of male to female patients, which was 2.4:1 for lymphoma in general, was approximately equal in the follicular group. This ratio may, however, be apparent only, since it is not borne out by the figures obtainable from the literature.

Fever of at least 100.5° F. was a relatively common observation in the miscellaneous group (42 per cent) and hyperpyrexia was not unusual. On the other hand, febrile manifestations were not common in the follicular group and in no instance was a very high figure attained. The possibility of an inflammatory background for these lesions was therefore not strongly substantiated.[4, 9]

Peripheral lymph nodes were enlarged with roughly an equal degree of frequency in both groups. Mediastinal masses were apparent more often in general lymphoma. Retroperitoneal and mesenteric nodes, however, showed involvement much more frequently in follicular lymphoma and often dominated the clinical picture. A common clinical syndrome consisted of ascites, edema of the lower extremities and scrotum or vulva, and palpable abdominal masses. As might be expected under the circumstances, ascites occurred with a slightly greater degree of frequency in the follicular cases. Peculiarly, among 13 with ascites, 9 of which were tapped, 7 proved to have chylous effusion. In the mixed lymphoma group there were 86 cases with ascites, only 7 of which were chylous. Splenomegaly occurred in one-third of the follicular cases and 40 per cent of the others; not a significant difference.

Cutaneous lesions were distinctly rare in follicular lymphoma. An occasional case showed a few isolated, raised, firm, brownish to reddish nodules. No diffuse lesions (mycosis fungoides) were observed although these constituted a significant proportion of the more common (21 per cent) skin affections noted in the larger group of lymphomas.

Intrinsic lymphomatous involvement of the lung, intestine or kidney was quite uncommon in follicular disease although varying degrees of obstruction as the result of extrinsic impingement upon the intestine, ureters, or air passages were observed. Even this, however, did not compare with the frequency of occurrence in the mixed group. In one instance only was there primary follicular involvement of the intestine without evidence of disease elsewhere and in no other case was the process primary except in lymph nodes. Two cases showed spinal cord symptoms as the result of encroachment by epidural tumor. In two patients there was breast involvement, two had testicular tumors, and in one each there was prostatic and tonsillar infiltration. Icterus appeared once only and was presumed to result from obstruction of the extrahepatic bile ducts by enlarged mesenteric lymph nodes. In all of these the visceral process appeared in the course of the systemic disease and though histologic confirmation was not available, characteristic response to irradiation was obtained. Orbital involvement was not observed.

Hematologic abnormalities were unusual. Anemia (3.5 million red blood cells or less) appeared in 18 per cent of the cases in contradistinction of 39 per cent of those with other types of lymphoma. Among the follicular patients, anemia generally occurred only as a terminal manifestation, and

was thought in some instances to represent the effect of long continued irradiation. Leukemia was not observed, although atypical white cells were present in small numbers in a few cases. Lymphocytosis and leukocytosis were sufficiently uncommon to be considered incidental.

Constitutional symptoms were not prominent features of follicular lymphoma. Recognition of the presence of the ailment usually occurred accidentally or as the result of secondary pressure phenomena. Herpes zoster appeared during the course of the disease in three cases. Four patients suffered from epithelial neoplasm in addition to lymphoma. Two had carcinoma of the skin, one of the cervix uteri, and one of the breast. Active tuberculosis was observed in two cases and the incidence of stigmata of healed disease did not exceed that of the population at large.

It is reasonable to conclude from a clinical point of view that the follicular form of lymphoma varies somewhat from malignant lymphoma in general. The process definitely affects an older group of individuals, it offers a far better prognosis, and remains for the most part limited to lymph nodes. There is considerably less tendency toward actual infiltration of adjacent tissues, metastasis is unusual, and hematopoietic complications not common. Retroperitoneal and inguinal lymph node involvement is quite characteristic, and as a result, edema of the lower extremities and chylous ascites are frequent concomitants.

Roentgenographic Observations

It was quickly evident that from the pure roentgenologic viewpoint there were no characteristic features distinguishing follicular lymphoma from the lymphomas in general. Most of the lesions noted by this means were readily apparent to routine methods of physical examination and the roentgen-ray findings were therefore merely confirmatory in character. In fact, in many instances roentgenologic studies were not performed since clinical examination sufficed.

For the sake of the completeness of this survey, however, certain observations are at least worthy of enumeration.

Sixteen of the cases showed roentgen-ray evidence of mediastinal masses. These were frequently lobulated and more common in the hilar regions. There was no predilection for either side of the chest and only occasionally were masses visible in the posterior or superior mediastinum. Pleural fluid was visualized in 13 patients and was slightly more common in the left chest. Intrapulmonary processes were observed three times; one of these proved to be tuberculosis, one was apparently bronchiectasis, and a third case was not autopsied but the pulmonary lesion was presumed to be lymphomatous.

Splenomegaly and hepatomegaly were each noted in six cases and in four cases intra-abdominal soft tissue masses were directly visualized. Abdominal films showed displacement of a kidney in four cases and in six there was unilateral hydronephrosis. Both of these observations were thought to

be the result of extrinsic retroperitoneal masses and revision to the normal state was apparent following roentgen treatment.

There was remarkably little evidence of extra-nodal disease. Pressure defects of the gastrointestinal tract were observed in four instances. In two cases intrinsic disease of the intestine was visualized but only one of these was found to be a primary tumor of the ileum at operation. The other represented invasive destruction of the cecum by ingrowing retroperitoneal tumor. Osseous lesions simulating metastatic neoplasm appeared six times and in four there was pathologic fracture. In none of these was there evidence of unrelated tumor elsewhere in the body and all responded adequately to irradiation.

Therapeutic Observations

Except for abdominal or thoracic paracentesis for the removal of accumulated fluid and an occasional case with a single localized lesion accessible to radical surgery, the treatment of choice in practically every case has been roentgen therapy. The basic treatment dose (lymphoma dose) was 600 roentgen units measured in air and derived from a 200 kilovolt generator. The operating distance was usually 50 cm. and the filtration 0.5 mm. of copper and 1.0 mm. of aluminum.

Treatment was administered in great part to regions with glandular enlargement, occasionally to the liver or spleen, and rarely over areas suspected of being the source of symptoms, although no lesions were evident to examination. " Spray therapy " was without perceptible value in our hands in this form of disease. It was therefore utilized infrequently.

Bone and visceral lesions and mediastinal and abdominal lymph nodes, the two latter particularly in the presence of effusion, generally required somewhat higher dosages of roentgens than were necessary to produce remission of peripheral processes. As much as 1200r to 1800r units to each of two fields were occasionally necessary to insure control of lesions. Following adequate therapy in follicular lymphoma, however, effusions often subsided without paracentesis and in several cases no need for therapeutic intervention arose for a year or more. Under similar circumstances hydronephrosis secondary to extrinsic ureteral pressure was also observed to recede rapidly. We have also observed bronchiectatic cavities caused by the compression of major bronchi completely relieved by roentgen therapy, both symptomatically and roentgenologically.

Experience with the therapeutic response of individuals severely dyspneic as the result of air passage encroachment has not borne out the traditional dictum that reactionary swelling of lymphomatous processes following roentgen-ray treatment frequently produced exacerbation of symptoms and even asphyxia. In follicular lymphoma immediate and dramatic regression was the rule and no exacerbations were observed. Small initial doses were given, however, as a precautionary measure.

Table IV represents the frequency with which poor results were obtained with irradiation in each of the various types of lymphoma. Lymphocytic and follicular lymphoma exhibited the greatest degree of radiosensitivity, only a rare instance of resistance being encountered. Stem cell lymphoma and reticulum cell sarcoma, although apparently only slightly less radiosensitive, required greater amounts of treatment (900r to 1200r) to obtain equivalent effects. So-called Hodgkin's sarcoma and lymphoblastic lymphoma (lymphosarcoma) not only required higher doses of irradiation but at least one-fifth of the cases failed to respond at all.

TABLE IV
Degree of Radioresistance

Type of Lesion	% Cases Resistant	
Lymphocytic lymphoma	3	
Follicular lymphoma	4	
Hodgkin's lymphoma	8	
Reticulum cell sarcoma	8	Require 900r to 1200r
Stem cell lymphoma	12	
Hodgkin's sarcoma	20	
Lymphoblastic lymphoma	21	

Complete records of roentgen therapy were available in only 29 of the 63 cases of follicular lymphoma. For purposes of comparison, 100 cases were chosen from the remainder of the malignant lymphomas. Selection of cases was based upon simple criteria. All had received roentgen therapy, all showed accessible lymph node lesions which could be used for the evaluation of therapeutic results, and all had sufficient follow-up data to permit conclusive opinions. Each had a predominance of lymph node involvement and minimal visceral or extranodal infiltration and therefore assured reasonably fair comparison. Analysis proved that these cases were susceptible to division into three major groups, each of which offered distinct prognostic implications associated with certain histologic variations. There was first the group of 29 cases with follicular lymphoma. The others, in view of the relative degree of malignancy evinced, were divided into an "intermediary" group (50 cases) with lesions classified as Hodgkin's and lymphocytic lymphoma, and a "malignant" group (50 cases) consisting of cases with reticulum cell and Hodgkin's sarcoma and stem cell and lymphoblastic lymphoma.

Grading of radiosensitivity was based upon observations of the response of palpable, visible, or visualized lymph nodes. Such response was determined as follows:

Excellent: Rapid and complete regression of adenopathy with very long intervals between recurrences.

Good: Early regression but rapid recurrence.

Fair: Slow regression, often requiring more than a single "lymphoma dose."

Poor: Little regression of symptoms or signs.

None: Progression of disease without abatement under treatment.

Additional features considered were the intervals between the regression of lesions and recurrences, symptomatic relief, and the duration of life after treatment. Figure 9, a composite graph in which all of these factors are considered, represents the character of response of the three groups of lymphoma enumerated above (follicular, "intermediary," "malignant"). Since the majority of the criteria of response indicated above varied in a distinctly parallel manner, they are all combined into a single curve for each group.

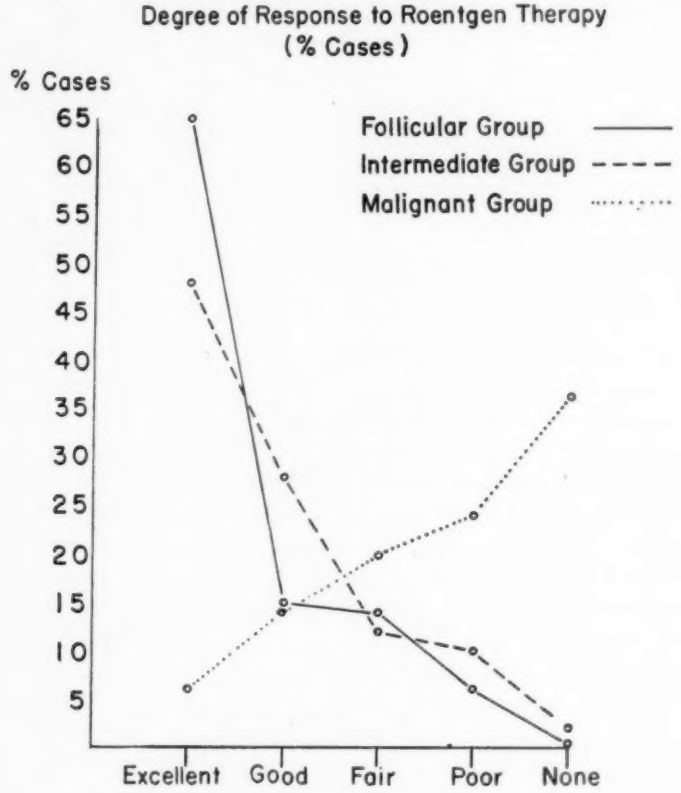

FIG. 9.

The superior efficacy of roentgen therapy in follicular lymphoma is readily apparent. In this category were the greatest number of complete regressions and none failed to improve under treatment. In the "intermediate" group fewer exhibited "excellent" results, and proportionately more showed fairly prompt recurrence of symptoms, but in general the therapeutic course was satisfactory. The "malignant" group showed a very distinct variation, however, the curve of response approximating a mirror image of the other two groups. A relatively high proportion of these cases manifested unimpeded downhill progression of the disease despite radiotherapy.

The incidence and rapidity of local and systemic recurrence closely paralleled the curve of response in the follicular and " intermediary " groups. The " malignant " types of lymphoma, however, varied somewhat unpredictably in this respect.

The duration of the disease following the initiation of therapy was 3.4 years in follicular lymphoma, 3.3 years with the " intermediary " group, and only 0.83 years for the " malignant " lesions. The similarity of prognostic outlook for the first two groups was apparent only, however, since the follicular cases showed symptoms of disease for an average of 2.7 years prior to the administration of roentgen-ray treatment and the " intermediary " group 1.6 years. The prebiopsy duration was even less for the " malignant " forms — 0.76 years. Although patients with follicular lymphoma appeared to survive for a period equal to that of the " intermediary " cases, medical aid was not sought until a much later stage of the disease. It is reasonable to infer that their earlier manifestations were decidedly milder. Furthermore, despite the delayed application of therapy, results were at least as favorable as those obtained in other forms of lymphoma and in most cases even more satisfactory (vide supra).

Summary and Conclusions

In an attempt to segregate follicular lymphoma from the general group of malignant lymphomas and to establish this disease as a lymphomatous entity a pathologic, clinical, roentgenologic and therapeutic analysis has been recorded.

Histologic studies have shown a distinct variation in structure from that observed in any other type of malignant lymphoma. In only one case was there morphologic evidence of the transition of a follicular process into what appeared to be another form of lymphoma. In all of the others there was abundant evidence, both morphologic and clinical, that certain variations in cellular arrangement and form were representative of a developmental pattern in the pathogenesis of the disease.

Clinical manifestations have been compared with those observed in 507 cases of known malignant lymphoma of varied types exclusive of follicular disease. Certain characteristic features have become evident. Individuals with the follicular process have exhibited initial symptoms at a much later period of life. The prognosis with regard to duration of the disease has been considerably longer with this group than with the remainder of the lymphomas. Constitutional manifestations and visceral involvement have been less frequent, and abnormal hematopoietic phenomena unusual. The apparently greater frequency with which retroperitoneal nodes become involved was impressive and the proportion of those cases with ascites which was chylous in character was considered to be of some diagnostic import.

Since only 29 cases had complete roentgenologic data, it was believed reasonable to select from the other types of lymphoma a sample (100 cases)

in which the clinical manifestations were quite similar to those present in follicular disease. No roentgenographic features with differential diagnostic significance were detected. From a therapeutic point of view the lesions in this form of lymphoma were much more susceptible to irradiation than those of the other groups. Immediate response occurred more frequently, recurrence was much slower in making itself apparent, and in no instance was there progression of symptoms under roentgen therapy.

All of these factors have caused the authors to conclude that follicular lymphoma, although a form of malignant disease of lymphoid tissue, has a distinct identity, with many characteristic clinical and structural features.

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ENDEMIC TYPHUS FEVER IN HAWAII *

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Introduction

A very interesting chapter has been added recently to our knowledge of a world-wide communicable disease, typhus fever. The investigations conducted in the southeastern United States, by members of the United States Public Health Service and by others, have proved that the form of typhus prevalent in this country is a disease separate and distinct from Old World or epidemic typhus. Reports from various parts of the United States and from other countries show large and apparently increasing incidence of the milder endemic form of typhus fever. This, of course, may be merely due to greater awareness on the part of physicians to the occurrence of the disease. Such probably is the case in Hawaii where the disease has been recognized only since 1933, although it undoubtedly was prevalent many years before this. An epidemiological study of the first 163 cases reported to the Territorial Board of Health and a clinical study of 33 local cases personally attended, is herein presented.

Historical Outline

Brill, in 1898, gave the first clinical description of endemic typhus fever. He applied the newly discovered Widal test to cases having typhoid-like symptoms and found 17 that gave negative agglutination. These cases all had similar symptoms; namely, a short course of fever with sharp termination in from 12 to 14 days and an extensive rash. Dr. Brill [1] continued his clinical investigations and in 1910 reported his findings in a total of 210 cases.

Maxcy and Havens in 1923 reported that cases of mild typhus similar to Brill's disease, occurring in the south, gave a positive agglutination reaction with Proteus X_{19}, a test found positive by Weil and Felix in 1915 in cases of epidemic typhus fever.

Maxcy [2, 3] continued his studies in the southeastern United States and made important observations regarding the epidemiology of endemic typhus. He pointed out that it was a disease of business establishments, particularly associated with grain or food handling places, and not of homes; that it did not select the poor and uncleanly; and that it was not associated with lousiness. He suggested that there existed some rodent reservoir (rats or mice) and that the transmission from this rodent reservoir might be by some insect vector.

The correctness of Maxcy's hypothesis was proved by the researches con-

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From The Clinic, Honolulu, T. H.

ducted by other members of the United States Public Health Service. Dr. Dyer and his associates, Badger, Ceder, Rumreich and Workman [4, 5, 6, 7] in 1931 and during the subsequent 12 months, published a series of papers which established beyond doubt the true epidemiology of endemic typhus. They showed that endemic typhus was essentially a disease of rats, and was transmitted from rat to rat, and occasionally from rat to man, by rat fleas (chiefly by *Xenopsylla cheopis,* but also by *Ceratophyllus fasciatus*). They showed, furthermore, that the virus multiplies enormously in infected fleas, and presented evidence suggesting the method of admission of the virus into animals by rubbing crushed infected fleas or infected flea feces into wounds made by bites of the flea or by scratching.

More recent work by Dyer and Brigham [8, 9, 10] has shown that other animals native to parts where typhus fever exists in endemic form are susceptible; for instance, mice, woodchucks, flying squirrels and cats. Moreover, infected field mice have been discovered in endemic foci. This suggests that reservoirs other than the rat may be, or may become, important in the transmission of typhus fever in the United States.

Epidemiology

Endemic typhus, according to present day teaching, is one of a group of related diseases caused by rickettsia.[11] The following classification by insect vector of the principal rickettsial diseases, is taken from the League of Nations Report on Typhus Fever [12]:

1. Epidemic typhus fever, human louse-borne typhus, exanthematous typhus, or Old World typhus, is a disease of humans, transmitted from man to man by the body louse. Its greatest incidence is in Central Europe, Asia, Africa and South America.

2. Endemic typhus fever, flea-borne or murine typhus, or Brill's disease, is a disease of rats and occasionally other rodents, transmitted from rat to rat and at times from rat to man by means of the rat flea. This group includes, besides American endemic typhus, Toulon ship-typhus, Hone's disease of Australia, Indian typhus ("Bangalore type"), tropical urban typhus or "shop" typhus of Malaya.

3. A third form of typhus fever is claimed by certain investigators to be alternately louse-borne and flea-borne. Mexican typhus (tabardillo) and Manchurian typhus belong to this group.

4. The mite-borne typhuses include tropical rural typhus or "scrub" typhus of Malaya, mite fever of Sumatra, Japanese river fever (Tsutsugamushi), Indian typhus ("X_k" type), and Queensland coastal fever. The reservoir in this group may be rats or field mice and perhaps birds, and a mite is the vector.

5. Tick-borne typhuses include Rocky Mountain and Eastern spotted fever, *boutonneuse* fever, Kenya tick-bite fever, South Africa tick-bite fever, Sao Paulo typhus, and Minas Geraes typhus.

Typhus in the United States

Old World or epidemic louse-borne typhus fever has never gained a foothold in the United States. The last true epidemic occurred in New York City in 1892–1893. Short-lived outbreaks were reported in New Mexico in 1922 and in Iowa and California in 1917. These last two were imported from Mexico.

A tick-borne rickettsial disease, spotted fever, has been known for a long time in the Rocky Mountain States. It was recognized in eastern states about the time the important epidemiological work on endemic typhus, previously recorded, was reported, and by the same group of investiga-

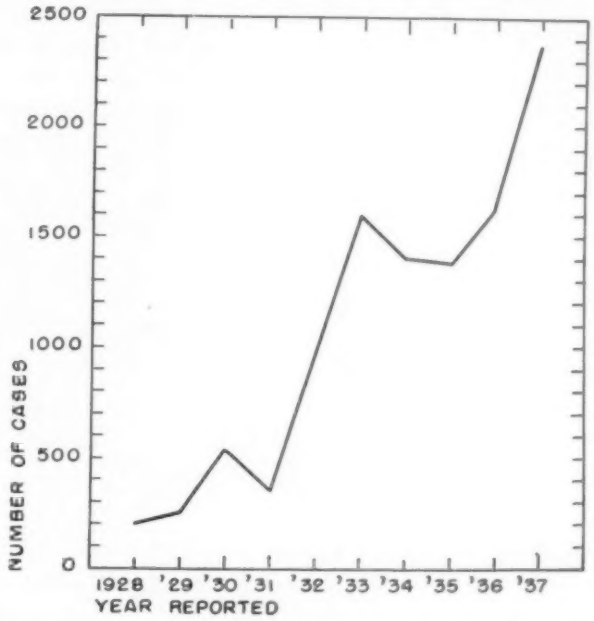

Fig. 1. Endemic typhus fever cases reported in the United States each year 1928–1937. This curve shows a marked rise from some 200 cases in 1928 to 2400 cases in 1937. The first rise between 1931 and 1933 is probably accounted for on the basis of the work of the United States Public Health Service which focused attention upon the disease and brought forth many new reported cases. The later rise, in 1936–1937, may be an index of actual increase in incidence. (Courtesy of the U. S. Public Health Service.)

tors.[13, 14, 15] The incidence of spotted fever in the United States, according to the League of Nations Report, was 197 cases in 1930; 213 in 1931; 421 in 1932; 467 in 1933; 405 in 1934; and 420 in 1935 (incomplete recording). Principal incidence is in Maryland, Virginia, District of Columbia, North Carolina, Montana, Idaho, Wyoming and Oregon.

Murine flea-borne or endemic typhus shows greater incidence than spotted fever. It is apparently increasing in the United States. This is best illustrated by the accompanying graph (figure 1) showing incidence of typhus in the years between 1928 and 1937.

The greatest yearly incidence of endemic typhus is in three states—Georgia, Alabama and Texas. Moderate numbers of cases are regularly reported in New York, Maryland, Virginia, North and South Carolina, Florida and Louisiana.

The spot map (figure 2) shows distribution of cases in the United States by county, up to 1937. This shows graphically the concentration of cases in the southern parts of the country. Maxcy previously called attention to the urban character of the disease. It more recently has been found also widespread in rural districts as shown by this spot map, and as commented on by Baker, et al.[16]

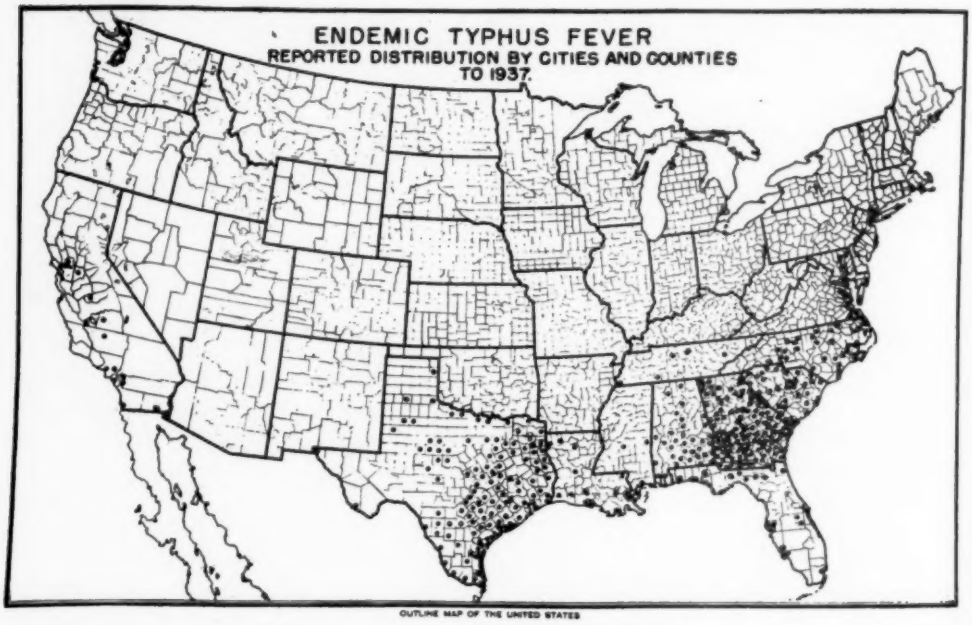

FIG. 2. (Courtesy of U. S. Public Health Service.)

Other important epidemiological features of the disease, as it occurs in the mainland of the United States, are:

1. A sharp increase in prevalence during summer and fall.
2. A relatively low incidence among negroes.
3. A low mortality rate, below 5 per cent in all communities, with the greatest number of deaths occurring in persons over 45 years of age.

ENDEMIC TYPHUS FEVER IN HAWAII

In the fall of 1933, the first case of typhus fever was reported in the Territory of Hawaii. Since that time and up to July 1, 1938, there have been recorded by the Board of Health 163 cases.

The disease undoubtedly was in existence here long before this time. Going back over our cases of mild or atypical typhoid having negative Widal,

shortly after our first case was proved positive, Dr. E. A. Fennel [17] found several from past years with a positive Weil-Felix reaction. It is reported that, as early as 1914, Dr. Jackson diagnosed cases treated in The Queen's Hospital in Honolulu, as having Brill's disease. Dr. Reppun, having attended large numbers of cases of epidemic typhus in Russia, reported a case as typhus fever to the Board of Health in 1921. Several cases similar to his occurred at the same time, and all recovered. It was decided by the authorities that the disease was not typhus fever.

That the disease now occurring in the Territory of Hawaii is actually typhus fever of the endemic type is proved by the following:

Protection tests, with serum obtained from an early case diagnosed as endemic typhus occurring in Honolulu, performed at the National Institute of Health at Washington, proved it to be typhus fever. Dr. Badger produced symptoms typical of typhus in guinea pigs inoculated with brain tissue of a rat trapped on the premises of another diagnosed case. There was thus established a strain in guinea pigs which later was shown at the National Institute of Health to be clinically and immunologically identical with their Wilmington strain of endemic typhus.

The *incidence* of endemic typhus in the Territory of Hawaii by county and by year is shown in the accompanying table obtained from the Territorial Board of Health.

TABLE I

Fiscal Years, July 1 to July 1

	1934	1935	1936	1937	1938	Total
Honolulu City	5	18	22	49	28	122
Rural Oahu	1	3	2	5	13	24
Total, Island of Oahu	6	21	24	54	41	146
Island of Hawaii	0	0	0	6	1	7
Island of Maui	0	0	7	0	0	7
Island of Kauai	0	0	0	0	1	1
Island of Molokai	0	0	0	0	2	2
Totals	6	21	31	60	45	163

The table shows cases occurring on all the larger islands. However, the majority of cases occur in the City of Honolulu, the only large urban community in the Territory.

Distribution of the first 89 cases reported in Honolulu is shown in the accompanying spot map (figure 3) copied after that of the Bureau of Communicable Diseases of the Board of Health. This map shows wide dissemination of cases. There is well-marked increased incidence over population density in outlying so-called better residential districts, as in Manoa and Kaimuki.

Rats trapped on or about the premises of cases of endemic typhus fever have been found to give positive Weil-Felix reactions. Guinea pigs inoculated with emulsions of fleas (*Xenopsylla cheopis*), combed from trapped rats, have developed certain suggestive febrile reactions and questionable

ENDEMIC TYPHUS
POSITIVE CASES — HUMANS •
— RATS ▪
After SHOT MAP
BUREAU of COMMUNICABLE DISEASES
TERRITORIAL BOARD of HEALTH
HONOLULU
ISLAND OF OAHU
TERRITORY OF HAWAII, U. S. A.
HONOLULU HARBOR
OAHU

FIG. 3.

scrotal lesions, and their blood serum was reported to agglutinate X_{19}. This cannot be accepted as proof of the existence of the disease in the rats though they were previously accepted as "positive" by the Board of Health. They are so designated on the spot map. There have been six such rats, of which three were *norvegicus,* one *alexandrinus,* one *rattus* and one unclassified. The majority of rats trapped about premises where typhus cases were reported were of the *norvegicus* (brown rat) type. For instance, among 87 rats trapped and classified during the period of three months, 72 were *norvegicus.*

The problem of rat harborage and food supply is a tremendous one in all parts of the city. In residential districts there are stone walls, chicken runs, abundant vegetation, and mango, cocoanut and avocado trees close to dwelling places. On nearby hillsides or vacant lots grow wild guavas, cactus, and other fruit-bearing plants. Complete eradication of rats is impossible.

Segregation of cases by *occupation* was made from reports available in the Board of Health. No predominance among persons engaged in any special type of work was noted. Maxcy, in his early studies of the disease in the southeastern United States, noted high incidence among workers in feed stores and restaurants. The data studied suggest that the most common source of infection in Hawaii is in or about the home.

Age. A study of 156 cases in which age was reported shows distribution by age groups as follows:

TABLE II

1 to 9 years	7
10 to 19 "	25
20 to 29 "	56
30 to 39 "	37
40 to 49 "	20
50 to 59 "	9
Over 60 "	2
Total	156
Age not stated	7
Total reported cases	163

The youngest reported case occurred in a child of two years and two months and the oldest in a 70 year old individual.

Sex. One hundred and five of the cases were males and 58 females.

Race distribution is as follows:

TABLE III

Caucasian	83
Japanese	22
Portuguese	20
Part Hawaiian	10
Filipino	9
Hawaiian	8
Chinese	6
Puerto Rican	4
Korean	1
Total	163

The composition of the population of the Territory at the mid-period, and the expected and actual numbers of cases of typhus fever for the period from July 1, 1934 to July 1, 1938, are presented in the following table:

TABLE IV

Race	Population*	%	Typhus Cases Expected No.	Typhus Cases Actual No.
Hawaiian	21,594	5.5	8.95	8
Part Hawaiian	37,608	9.6	15.6	10
Portuguese	29,863	7.6	12.4	20
Puerto Rican	7,470	1.9	3.1	4
Spanish	1,261	0.3	0.5	0
Other Caucasian	57,069	14.5	23.65	83
Chinese	27,495	7.0	11.4	6
Japanese	149,886	38.1	62.1	22
Korean	6,682	1.7	2.3	1
Filipino	53,550	13.6	22.2	9
Others	799	0.2	0.3	0
Total	393,277			163

* Board of Health estimate for June 30, 1936.

Though actual statistical correlation is not presented, these figures show obvious excess of cases over expectancy in the large group of "Other Caucasians," which is comprised chiefly of American whites. There is a notable reduction in cases over expected numbers among both Japanese and Filipinos. These differences may be due partly to residence. The largest concentration of whites in the Territory is in the City of Honolulu. A larger proportion of Filipinos and Japanese still remain in the rural communities.

A study of the disease by quarters in the Territory of Hawaii and in three states of the United States is presented in the following table:

TABLE V

	1934				1935				1936				1937			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Hawaii	1	1	7	9	1	3	7	17	7	2	10	29	11	2	10	10
Georgia					40	69	219	139								
Alabama					20	51	141	80								
Texas					34	36	94	72								

This table shows that the incidence of the disease in Hawaii rises, as it does elsewhere, in the summer and fall months. The disease tends, however, to have continued prevalence here during the winter months as well.

Up to the present time, only one fatality has been recorded as due to typhus fever in Hawaii.*

EPIDEMIOLOGY AND SYMPTOMATOLOGY OF LOCAL CASES

A. Epidemiology

There is presented herein a study of 33 cases personally attended, in the great majority of instances with complete home or hospital supervision car-

* One more death has occurred in the Territory of Hawaii since the publication of Board of Health reports for the fiscal year ending July 1, 1938.

ried out by the author. A summary of the individual cases is given in the following table.

Data on symptoms, both subjective and objective, laboratory tests, et cetera, are incomplete in many instances. This is because some patients were cared for in the home where observations and laboratory examinations were limited, and also in some instances because of inadequate notes on hospital cases. The small number of cases further limited the value of the tabulation. However, since the review was made by the same person who observed all of the cases, and since the clinical side of the disease was his chief interest, it was felt that the data were worthy of study.

Distribution of Cases. Of the 33 cases studied, 22 were treated at some time during the acute illness in the hospital and 11 were cared for at home throughout the illness. Sex distribution between sexes was almost equal. Seventeen were males and 16 were females. The racial distribution is recorded in table 7.

Age distribution was wide, the youngest case being a child of 10 years and the oldest a man of 58 years. There were 12 cases below 20 years, 14 between 20 and 39, and 7 of 40 or over.

Epidemiological Features. The majority of our cases apparently were exposed to infection about the home. Our patients came from all sections of the city, but more lived in outlying residential districts than in downtown congested areas. Many had good places for rat harborage in chicken houses or stone walls on their lots. Many noted the presence of rats about the premises. In several instances, sick or dead rats were observed or handled. Frequently, several cases were reported in the immediate neighborhood within a period of a few days or weeks. Two families had multiple cases occurring at approximately the same time.

The "B" family lived in an open, rambling house on a dry hillside. The lot was poorly cleared, had chicken houses close to the house and rock piles about. Rats were seen and heard frequently. The first patient in the family became ill on October 2, 1934, and his brother became ill on the seventeenth of the same month. Another case, living less than half a block away across the street and below them on the same hillside, but having no personal communication, was seen October 12, having begun three or four days previously.

In the "J" family there were three cases which occurred at approximately the same time, and there was another case across the street during the same month. The neighbor's cat had recently brought a dead rat on the front porch. The children fondled and played with their own and the neighbors' cats inside and out of the house. The first patient, a girl of seven years, became ill about October 12, 1936, and was first seen on October 17. This same day the mother and brother became ill. Neither of the children had a noticeable rash, but the mother had a typical rash on the fifth day. The boy's illness was quite mild. He was never entirely confined to bed, and fever lasted only a little over a week. All had positive Weil-Felix agglutination tests.

Incubation Period. The incubation period is difficult to estimate. Dyer, Rumreich and Badger [13] say, "In the few cases in which the probable incubation period could be estimated, it varied from seven to fourteen days."

TABLE VI

No.	Date Month/Year	Treated Home—H Hosp.* No.	Sex	Age	Race	Symptoms: Onset Acute Prodromata	Symptoms: Headache Day†	Symptoms: Body Aches	Symptoms: Chills	Symptoms: Other	Eruption Occurred Day*	Temp. Max. Day*	Temp. Normal Day*	Laboratory: Urine Alb.	Laboratory: Other	Laboratory: Wbc. Thous. Day‡	Laboratory: Polys. %	Laboratory: Weil-Felix Dil./Day*	Severity	Complications and Notes
1	9/33	Q 81,874	F	58	Port.	+	+/10	+	0	Diarrhea Cough	+/9	104	19	Tr.	0	10.4/10	78	1:5120/42 1:320/150	Mod.	
2	12/33	H	F	50	Port.	?	+	+	−	−	+/7	103 ?	18	++	C & F G casts	−	−	1:2560/13	Mod.	
3	7/34	Q 86,960	M	15	Chin.	?	+	?	?	Cough	?	?	?	0	0	7.8/22 ?	63	1:2560/27 ?	Mod.	
4	9/34	St. F. 7886	M	23	Haw.	?	+/14	?	?	−	?	103 ?	20	Tr.	Wbc.+ Rbc.+	6.6/7	50	1:2560/14	Mod.	
5	11/34	Q 88,715	M	26	Jap.	++	+/12	+	+	Epigastric pain	+/6	104	14	0	−	9.6/5	76	1:2560/9	Mod.	
6	1/35	H	F	50	Port.	+	+	+	+	−	+/7	103	12	Tr.	Wbc.++ Rbc.+	4.8/5	64	1:320/22	Mod.	
7	6/35	Q 92,535	F	15	P. R.	?	+/12	++	−	Muscle pain Hyperesthesia	+/4	104.5	14	+	−	8.9/4	84	1:640/12	Mod.	Secondary anemia
8	10/35	St. F. 9237	M	18	Port.	+	+/17	+	+	Vomiting Abdom. pain Epistaxis	0	103.8	17	0	Sug.+	9/3	72	1:5120/15 1:10,240/21	Mod.	Furunculosis
9	10/35	H (Brother of 8)	M	15	Port.	+	+	+	+	Chest pain	?	103.8	?	−	−	−	−	1:2500/8	Mod.	Furunculosis
10	10/35	Q 94,866	F	30	Cauc.	+	+/10	+	−	Chest "constriction," cough and night terrors	+/8	104	15	+	Wbc.+ Rbc.+	7.3/10	78	1:640/12	Mod.	
11	2/36	Q 97,546	M	24	Cauc.	+	?	?	+	Abdom. pain Diarrhea	?	104.2	16	0	Wbc.++	14.4/8	66	1:2560/16	Mod.	
12	3/36	Q 97,680	F	20	Port.	+	+/12	?	+	Abdom. pain Diarrhea	+/8	103.8	16	Tr.	Rbc.+++	8.3/8	56	1:1280/12	Mod.	
13	6/36	Q 99,956	M	55	Cauc.	+	+/16	+	+	Cough, vomiting, delirium and frequency	+/7	105	22	+	Wbc.+	5.9/8	80	0/9 1:160/10 1:5120/17	Severe	Pyelitis
14	8/36	Q 100,880	F	14	Jap.	?	+	+	−	−	+/4	104.2	15	0	0	5.6/5	54	1:20/7 1:1280/12	Mod.	
15	8/36	Q 101,012	F	33	Cauc. Haw.	+	+/12	+	+	Vomiting Abdom. pain Diarrhea	+/8	102.6	15	0	0	7.45/3	76	1:20/10 1:160/14 1:320/16	Mod.	

* Hosp.—Q—The Queen's; St.F.—St. Francis; C—Children's.
† Day—The day of the illness.
‡ Several cases had repeated blood counts as recorded in table 8 but only one is recorded here

TABLE VI—*Continued*

No.	Date Month / Year	Treated Home—H Hosp.* No.	Sex	Age	Race	Symptoms: Onset Acute Prodromata	Symptoms: Headache / Day†	Symptoms: Body Aches	Symptoms: Chills	Symptoms: Other	Eruption Occurred Day*	Temp. Max. Day*	Temp. Normal Day*	Laboratory: Urine Alb.	Laboratory: Other	Laboratory: Wbc. Thous. / Day‡	Laboratory: Polys. %	Laboratory: Weil-Felix / Dil./Day*	Severity	Complications and Notes
16	9/36	C 13,644	F	10	Cauc.	+	?	?	−	−	+/4	104.8	16	0	−	9.2/6		0/7	Mod.	
17	9/36	Q 101,914	F	32	Cauc.	+	+/15	+	+	Vomiting	+/?	103.8	16	+	Sug.+	6.7/9	75	1:640/14 1:20/10	Mod.	
18	10/36	H (Daughter of 19)	F	7	Cauc.	?	0	0	0	Fatigue	0	102	?	0	Rbc.+	9.5/9	44	1:640/14 0/9	Mild	
19	10/36	H	F	32	Cauc.	+	+	+	−		+/5	102	?	−	−	−	−	1:640/42		Three cases in the same family
20	10/36	H (Son of 19)	M	12	Cauc.	?	+	0			0	?	?	−	−	−	−	1:1280/21	Mod.	
21	1/37	Q 103,676	M	19	Jap.	+	+/7	+	+	Disturbed sleep Epistaxis	0	102	9	+	Wbc. Rbc. F. G. casts few	7.5/4	88	1:320/36 1:160/12	Mild Mod.	
22	1/37	Q 103,817	M	51	P. R.	?	+	+	+	Vomiting	+/?	103.4	?	Tr.	Wbc. few	12.2/?	83	1:2560/?	Mod.	
23	1/37	H	M	22	Jap.	+	?	+	?	Epistaxis Cough	0	103	?	++	C G casts few	−	−	1:1280/8	Mod.	Toxic thyroid
24	7/37	Q 107,814	M	17	Cauc. Chin.	+	+/11	+	+	Conjunctivitis	+/6	104.6	15	0	0	5.2/6	58	0/6 & 8	Mod.	
25	9/37	Q 109,222	M	16	Cauc.	+	+/16	+	+	Disturbed sleep Cough	+/8	104.2	19 ?	0	0	10.7/8	74	1:1280/10 0/10	Mod.	
26	9/37	Q 109,999	F	49	Port.	+	++/12	+	+	Conjunctivitis Photophobia Vertigo	+/8	103.6	16 ?	0	0	7.8/8	83	1:1280/14 1:640/10	Mod.	
27	10/37	H	M	40	Cauc.	+	++/13	?	−	Chest constriction, vertigo, vom. and diarrhea, disturbed sleep	+/7	102.5?	13 ?	−	−	−	−	1:640/11	Mod	
28	12/37	Q 111,474	M	44	Jap.	+	+/14	+	+	Insomnia Nervousness	+/8	102.8	14	++	Wbc. Hy. casts few	−	−	1:1280/11	Mod.	
29	12/37	H	F	19	Jap.	+	+/14	+	+	Vomiting	+/4	103	16 ?	−	−	6.2/6	64	1:320/6	Mod.	
30	4/38	Q 114,095	M	17	Fil.	+	++/4	+	+	Insomnia	0	101.6	8	+++	Wbc. few C G casts+	10.8/4	88	0/8 1:320/11	Mod.	
31	5/38	H	M	25	Cauc. Haw.	+	+/10	+	+		+/7	104.6	17 ?	−	−	−	−	1:3200/13	Mod.	
32	5/38	H	F	18	Cauc. Haw.	+	+/12	+	+	Cough	+/5	104	?	−	−	−	−	1:640/12	Mod.	
33	6/38	Q 115,821	F	27	Cauc.	+	0	+	+		+/?	104.6	?	+	Wbc.+	7.7	82	1:1600	Mod.	

In one case, C. V. F., this period appeared to be established by the following history: The illness began abruptly just two weeks (14 days) after handling a dead rat. The time was accurately set by checking the day of garbage collection. The patient had found the dead rat in the front yard and had carried it to the rubbish cans which were out in front for mid-week collection.

B. Symptoms

Onset. The onset of the disease, according to Maxcy [18] and to Rumreich, Dyer, and Badger,[14] is usually abrupt. The illness is ushered in with chills or chilliness, fever, malaise, headache, anorexia and prostration. Maxcy recorded abrupt onset in 65 per cent of his series reported in 1926. Blatteis [19] noted gradual onset in 42 per cent of 136 cases studied in 1928. Brill found frequent prodromata of three to four days' duration.

Twenty-two of the 33 local cases studied had an onset which was recorded as acute, while eight cases had inadequate data to record the mode of

TABLE VII

Portuguese	7
Other Caucasian (this included one Caucasian-Chinese)	12
Japanese	6
Hawaiian and part Hawaiian	4
Puerto Rican	2
Chinese	1
Filipino	1

onset. Three cases had definite prodromata or gradual progression of symptoms recorded.

First symptoms generally were recorded as " 'flu-like." Headache, body aches, anorexia, chills and fever were the most frequent early symptoms. Headache was recorded in 22 cases, body aches in 18 and chills in 12. Other early symptoms were fatigue, dizziness, constipation, " gas," diarrhea, disturbed sleep or insomnia, sore throat, " tightness of the chest," and cough.

General Symptoms. (*a*) Headache is recorded as an outstanding symptom by all authors. Brill says, " Headache is one of the most pronounced features of the disease and is almost invariably present." In his series of 50 cases, it was stated to be agonizing in 8, intense in 33, and moderate in 9. He says the headache is general, likens it to the headache of meningitis, and notes rigidity of the neck and positive Kernig occasionally in the most severe cases.

Headache was the outstanding single symptom in our series. It usually occurred at the onset. Occasionally, other general symptoms, tiredness, malaise, and body aches, overshadowed the headache and lasted longer. This was more frequent in younger persons. Headache was recorded as definitely present at some time during the course of the illness in 28 of the 33 cases studied.

The headache was recorded most commonly as frontal, though sometimes it was occipital and sometimes diffuse. The pain was frequently intermittent, increasing greatly in intensity as the fever rose. Ordinarily, the headache persisted nearly as long as the fever. Either it was not present or the duration was not determined in 13 cases. Of the 20 remaining cases, 2 had headache for a week or less, 14 up to two weeks, and 4 over fourteen days.

Relief was obtained sometimes by ice cap alone. Usually, aspirin and codeine combined were required in adults for any degree of comfort. Morphine was given in a few cases at the height of symptoms. A recent case seemed to be afforded relief by hypertonic dextrose (40 to 50 c.c. of 50 per cent solution) administered intravenously, and one case had abrupt cessation of headache following lumbar puncture.

(*b*) Body aches and pains. Maxcy stated that pains in the back of the neck, lower back, and calves of the legs were common and that general body aches were muscular rather than in joints. In our series, muscular and joint pains were frequent and were more marked than those of other infectious diseases, except influenza. These pains were noted in the extremities more frequently than in the back. The aching pains seemed to be interpreted by children merely as a marked sense of tiredness or fatigue. Rarely a feeling of aching in the chest or abdominal muscles focused attention for a short time on organs of these regions.

Twenty-five of our cases had body aches or pains recorded as a symptom. The duration was shorter than that of headache, usually marked only during the first three or four days. One case, M.G., a 15 year old Puerto Rican girl, had unusually severe body aches, joint and muscle pain and hyperesthesia, persisting to the twelfth day. There was associated in this case an unusual secondary anemia, which may have contributed to the severity and duration of these symptoms.

(*c*) Chills were frequent but irregular in intensity and in occurrence. Frequently they occurred as a first symptom but were of less startling intensity than those of pneumonia or of malaria. Recurrence was irregular, not daily but perhaps two or three times the first week and once or twice after that in a case of average severity. Chilly sensations were more frequent. Both chills and chilly sensations attended the wider temperature fluctuations which occurred. Twenty of our 33 cases had chills recorded at some time during the course of illness.

(*d*) Diaphoresis was recorded in 14 of our cases. The sweats occurred irregularly, either related to wide temperature fluctuations or during the stage of defervescence of fever. Sometimes they persisted to the fifteenth day of illness or occasionally longer.

Gastrointestinal Tract Symptoms. Brill stated that constipation was a marked feature of his cases, being present in 42 of 50 cases intensively studied. In two cases, diarrhea followed a previous constipation. Tympanites was not a feature. Maxcy noted " nausea for a few days, followed

by aversion to food to convalescence"; coated tongue, bad breath, and constipation, with a flat abdomen.

Anorexia was present in practically every case in our series and generally persisted as long as the headache and fever. Vomiting occurred most frequently during the early stages of the disease. It was recorded in seven cases of our series. Diarrhea was recorded five times. It consisted of from two to four loose stools a day and abated by the end of the first week. Constipation was a more frequent complaint, particularly during the early stages of the disease. Either constipation or diarrhea was attended at times by abdominal discomfort. This was recorded as a noticeable symptom in eight cases. "Gas" usually was relieved by simple enemata, and distention was never a troublesome feature of the illness.

Respiratory Symptoms. Brill stated that bronchitis was a common accompaniment of the disease.

Cough occurred in five of our cases. In two of these cases it persisted to the tenth and fourteenth days, respectively. Chest pain occurred only as a part of the general muscle aching. Two individuals complained of a peculiar sense of constriction of the chest at onset. Mild sore throat was sometimes present during the early stages of the disease. A definite pharyngeal or tonsillar injection was the only commonly noted physical sign on first examination. Epistaxis was recorded in three cases.

Genito-Urinary Symptoms. Frequency, associated with pyuria, was recorded in two cases. Dysuria was experienced occasionally by patients, but was believed to be due principally to codeine or morphine administered to control the headache.

Central Nervous System Symptoms. Brill emphasized the mental apathy and dulled sensorium as outstanding symptoms but stated that a mild muttering delirium was present only occasionally. Maxcy recorded delirium in 28 per cent of his cases and stated that other symptoms were apathy and mental dullness, increased nervous irritability, and night terrors. Dyer, Rumreich and Badger noted the same symptoms but stated they were much less marked than in cases of Rocky Mountain spotted fever. Delirium, in their experience, was not usually severe.

Increased irritability or depression, insomnia, and unpleasant dreams were fairly common in our experience. True delirium occurred but was not frequent. It was severe in only one case, R. H. W., a 55 year old Caucasian male.

Case Report

R. H. W., 55 year old Caucasian male, was first seen June 27, 1936. He was admitted to The Queen's Hospital on June 29, 1936, and discharged July 13, 1936.

Epidemiological Features. There was a rock retaining wall back of the house, with many rat holes and swarms of rats. The patient also stated that he had noticed rats about his office and made many visits to shops and mills which were rat infested.

Clinical Features. The onset, five days before time of first visit, was manifested by a feeling of general malaise and tiredness. He continued to work until the

evening of the fifth day of illness when his temperature went up to 103°, he became extremely weak and had very severe generalized muscle and body pains. During that night he became delirious. First visit was made the next day, at which time there was a temperature of 104°, and a dry tongue was noted. Rash occurred on the seventh day. This was characterized as macular. It occurred first on the lower chest and by evening had spread to the middle of the back. The next day it had spread over the upper back, then involved the arms, thighs, particularly the inner surface, and by the tenth day it had spread well over the neck, legs, forearms and finally the feet. Rash was extensive and marked, but never became petechial, although the stains of pigment deposit remained for a number of days after the rash cleared.

Course in Hospital. This was unusually severe, and was marked by excruciating headache, and delirium at night. These symptoms continued through the eighteenth day of illness. There were recurring chilliness and diaphoresis. There was some cough and occasional vomiting. Frequency was present after the fourteenth day.

Laboratory Findings. Urine showed 1 plus albumin on the ninth, seventeenth and twenty-second days, with scattered white blood cells. After discharge, there continued to be albuminuria and pyuria, and a cystoscopic examination on July 28 revealed bilateral pyelitis and cystitis, with *B. coli* the causative organism. The white blood cell count on the eighth day was 5,900, with 80 per cent polymorphonuclears, 3 per cent monocytes, 16 per cent lymphocytes. Two days later, white blood cells numbered 4,400, with 86 per cent polymorphonuclears. Weil-Felix was negative on the eighth and ninth days, became positive in a dilution of 1 : 160 on the tenth day, and on the seventeenth day was positive in dilution of 1 : 5120.

This was the most severe case observed. The clinical course was marked by high fever, recurring chills, prostration and delirium. A pyelocystitis complicated the case.

Spleen. The spleen was noted as distinctly palpable below the costal margin in 27 of the 50 cases Brill reported. Blatteis found it in 28 per cent of cases reviewed. Rumreich, Badger and Dyer noted it only twice, and Maxcy stated that it was rare. We did not note a palpable, enlarged spleen in any of our cases.

The Eruption. The rash has been well described by Brill, Maxcy and by others. It is a maculopapular eruption. Lesions are small, measure 2 to 4 mm. in diameter, and are dull red or pink in color, irregularly round or oval, having ill defined margins, and fading on pressure. Onset is between the fifth and seventh days of illness. Rumreich, Dyer and Badger said it occurred almost invariably on the fifth day. The site of first appearance is generally the lower chest and abdomen. Spread is to mesial surface of arms, shoulders and back, then to thighs and sometimes lower arms and legs. Involvement of face, palms and soles is extremely rare.

Our cases showed eruption of this general pattern. The intensity and duration varied considerably. No rash was seen in 10 of the group studied. Six of these had too inadequate study to say that there had been no eruption, but four were observed in the hospital from the fourth or fifth day of illness. Not all were dark-skinned individuals.

The time of onset of rash, in our series, was a little later than noted above. In 20 cases where the day of onset of rash was stated, it was first

noted on the fourth day of illness in 4, fifth day in 2, sixth day in 2, seventh day in 5, eighth day in 6, and the ninth day in 1. Ordinarily, the rash disappeared in from four to eight days.

Temperature. Maxcy and Rumreich, Dyer and Badger gave good descriptions of the temperature course. They noted a step-like progression of fever, with usual daily remissions of from one to three degrees, to a maximum on the fifth to tenth day. During the second week, the remissions more nearly approximated normal, the daily rise became less marked, and by the fourteenth day the temperature failed to rise and there was marked relief of symptoms. Defervescence was usually by rapid lysis. Brill reported fall by crisis in 16 cases, by rapid lysis (less than 48 hours) in 17 cases, and by lysis in 17 cases. Brill noted less marked fluctuations of temperature, and stated that remissions usually were less than one degree.

Our cases showed frequent and well marked fluctuations of fever. Sometimes two waves from 99° or 100° F. to 103° or 104° would occur in a single 24 hour period. There generally were wider fluctuations of temperature toward the end of the first week of illness, at the time the rash appeared. The average maximum fever was between 103° and 104°. In 31 cases the maximum recorded temperature was as follows: 102° or less, four cases; 102.2° to 103°, eight; 103.2° to 104°, ten; 104.2° to 105°, nine. No cases had fever over 105°. The maximum was usually reached in the first week, sometimes during the first three or four days. Daily elevation of fever to this degree ordinarily persisted to the tenth or twelfth day, then a rapid or slower lysis occurred, with return to normal by the fifteenth or sixteenth day of illness.

Pulse. The pulse was slow in relation to height of temperature. There was no bradycardia as in typhoid, nor was any unusual character of pulse recorded. The average pulse rate during the febrile period ranged between 80 and 100.

Case Reports

J. A., a Japanese male, aged 26 years, was first seen November 9, 1934, and was admitted to The Queen's Hospital on November 11 and discharged on November 20.

Clinical Features. The patient had become acutely ill three days before the first visit. His complaints were headache, which was severe and throbbing in character "as though his head would burst," chilliness, fever, sweats and dry throat. Lumbar pain had been present at the onset, but none was complained of at time of first visit. There had also been burning epigastric pain and anorexia. Headache and prostration were so severe as to make one suspect meningitis. Neurological examination was negative, nor were there any other abnormal findings except a heavily coated tongue. Temperature was 102° F. at time of first visit. The next two days at home the fever ranged between 100° and 104°. On the sixth day of illness a rash was noted and on this date he was admitted to the hospital.

Course in Hospital. Temperature course (including several temperatures taken at home before admission) is presented in the accompanying chart (figure 4). It shows irregular high temperature persisting through the tenth day. There was a critical drop on this day, but a daily rise to about 100° continued until the fourteenth day.

Headache was severe and persisted through the tenth day. Chills were recorded twice. Drenching sweats recurred with the fall of temperature on the tenth day and continued through the twelfth day of illness.

Laboratory Findings. Urine on the fourth day of illness was negative. Blood count on the fifth day of illness showed 9,600 white blood cells and 76 per cent poly-

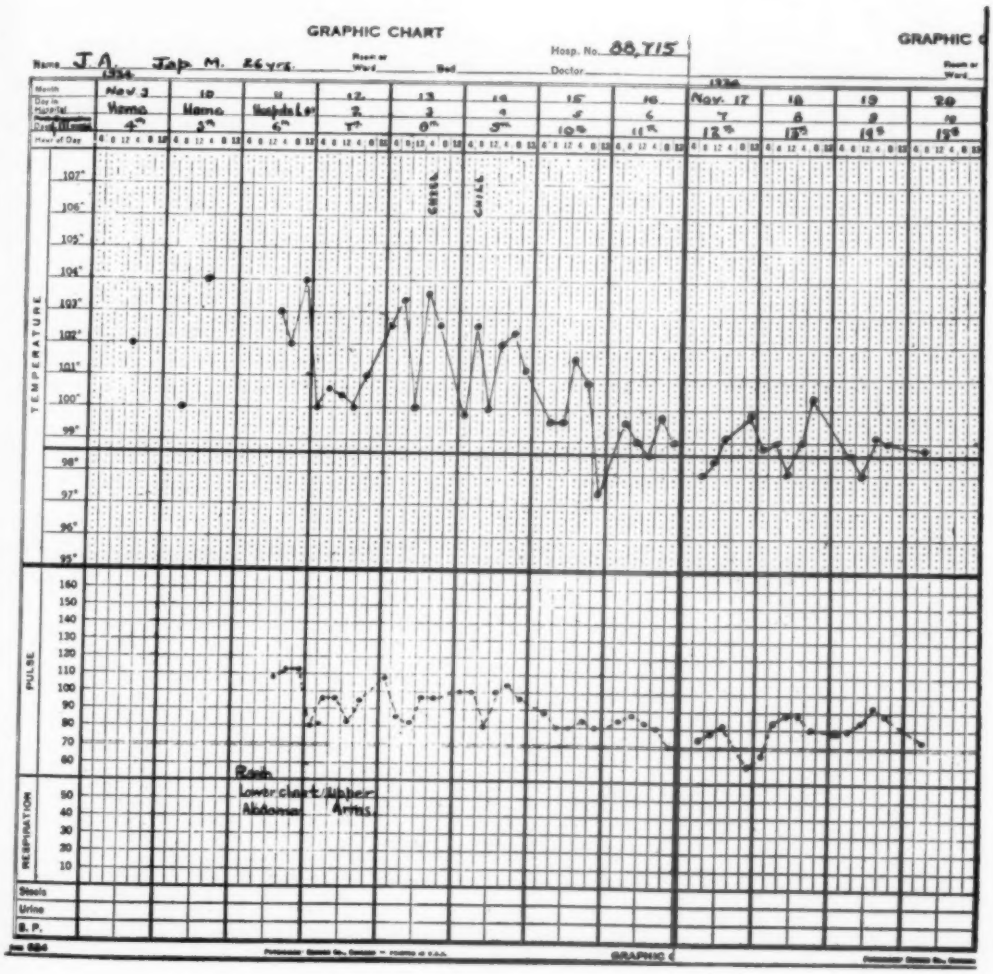
GRAPHIC CHART
Name J.A. Jap M. 26 yrs.
Hosp. No. 88,715
Doctor
1934
1935
Nov 3 10 11 12 13 14 15 16 Nov. 17 18 19 20
Hemo Hemo Hemo 2 3 4 5 6 7 8 9 10
4th 5th 6th 7th 8th 9th 10th 11th 12th 13th 14th 15th
Hour of Day
TEMPERATURE
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°
CHILL
CHILL
PULSE
160 150 140 130 120 110 100 90 80 70 60
RESPIRATION
50 40 30 20 10
Rash
Lower chest/Upper Abdomen
Arms
Stools
Urine
B. P.
GRAPHIC

FIG. 4.

morphonuclears. On the twelfth day of illness, white blood cells numbered 7,000 with 72 per cent polymorphonuclears. Blood culture taken the same day was negative, and culture of urine for *B. typhosus* was reported negative on the eleventh day of illness. Weil-Felix test was positive in a dilution of 1 : 640 on the ninth day of illness.

A. B., Portuguese male, 18 years old, was first seen on October 4, 1935. He was admitted to St. Francis Hospital on this date and was discharged October 23, 1935.

Epidemiological Features. This was the first of a series of three cases occurring in his immediate neighborhood. The boy lived in a rambling open house on the side

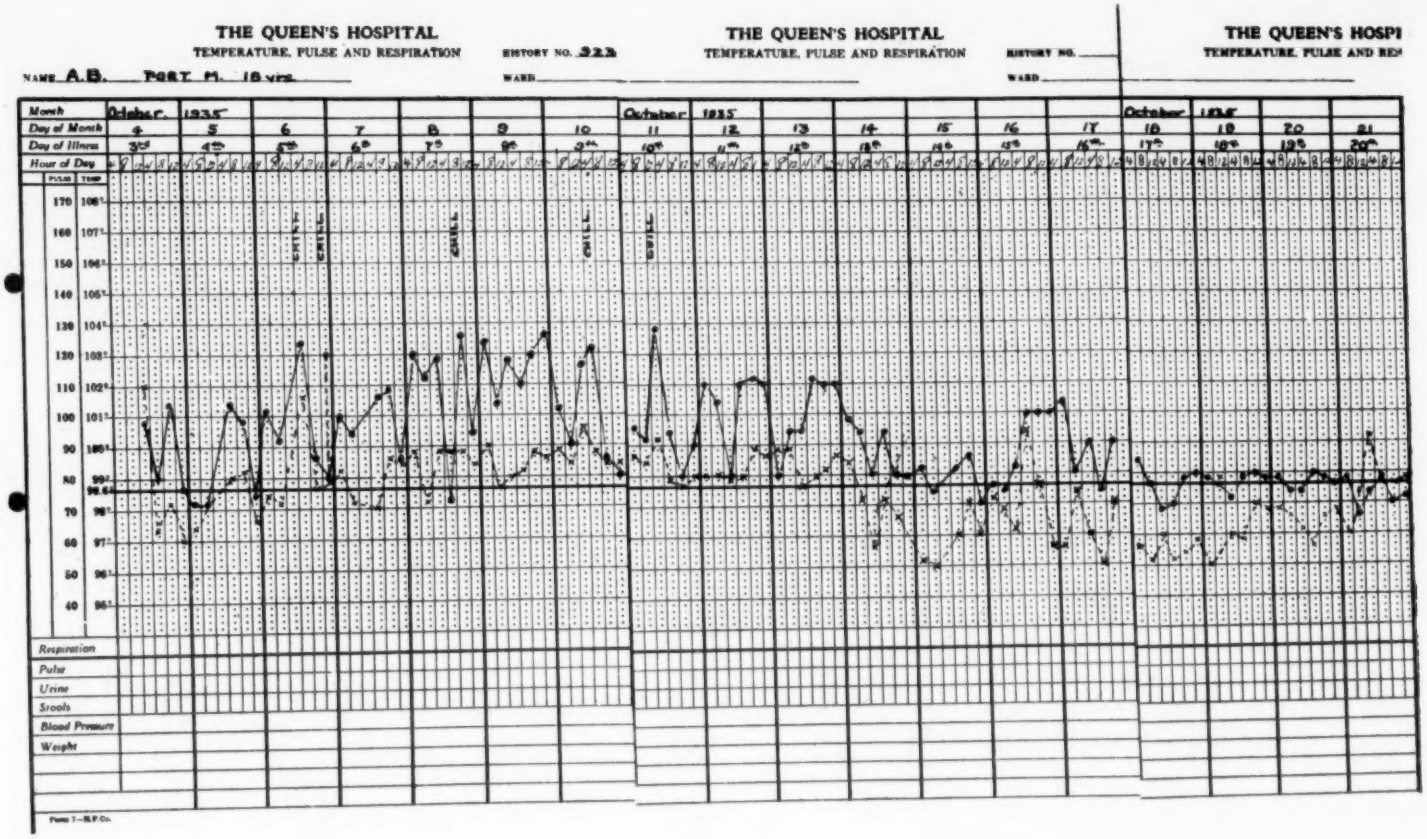
THE QUEEN'S HOSPITAL
TEMPERATURE, PULSE AND RESPIRATION
HISTORY NO. 923
NAME A.B. Port M. 18 yrs.
WARD
THE QUEEN'S HOSPITAL
TEMPERATURE, PULSE AND RESPIRATION
HISTORY NO.
WARD
THE QUEEN'S HOSPI
TEMPERATURE, PULSE AND RES
Month
Day of Month
Day of Illness
Hour of Day
October 1935
CHILL
Respiration
Pulse
Urine
Stools
Blood Pressure
Weight

FIG. 5.

of a hill. The family kept chickens, had many birds and animals about the place and there were many rats running around the rocky hillside.

Clinical Features. The onset had been "'flu-like," with aching body pains two days before the first visit. His temperature was 101.4° F. at the time of the first examination. Headache was a prominent symptom. Temperature in the hospital was septic, varying between 98.6° and 103.8° up to the tenth day of illness. On the eleventh day and on the twelfth day, the temperature was 102.2° and dropped to 99.6° on the fourteenth day, then fluctuated to 101.4° up to the sixteenth day and on the seventeenth day dropped to 99.4° and did not rise above 99° thereafter (figure 5).

Headache persisted to the sixteenth day, chills recurred irregularly to the twelfth day and diaphoresis was marked through the nineteenth day of illness. There was some abdominal pain and occasional vomiting. Epistaxis occurred twice. A furuncle of the face required opening on the ninth day of illness. No rash was recorded, although examination was made regularly during the hospital stay between the third and twenty-first days of illness.

Laboratory Findings. On the third day of illness, white blood cells numbered 9,000. On the seventh day, white blood cells numbered 6,200 with 68 per cent polymorphonuclears, 32 per cent small lymphocytes. On the thirteenth day, white blood cells were 8,600 and polymorphonuclears 72 per cent. The stool was negative for typhoid and paratyphoid bacilli on the ninth day of illness. Blood agglutination tests for typhoid, paratyphoid A, B, and *B. abortus* were negative on the seventeenth day. Weil-Felix test was positive up to dilution of 1 : 5120 on this date and became positive to dilution 1 : 10,240 on the twenty-second day of illness. Urine was negative throughout the course.

C. Laboratory Findings

Urine. The urinary findings were those which accompany any febrile illness. Albumin was recorded as more than a trace in 10 of the 26 cases where this examination was made. When present it usually cleared by the tenth day of the disease. White blood cells in numbers greater than a few occurred in six cases, red blood cells in five, casts in five and sugar in two cases. One case, R. H. W., had albumin and cells persisting into convalescence. A cystoscopic examination in this case showed *B. coli* pyelitis.

Leukocyte Count. Brill noted that there was no leukopenia in this disease, and the average white blood cell count in his series was between 9,000 and 11,000. He noted an average count of polymorphonuclears of 69.4 per cent and lymphocytes 30.6 per cent.

Table 8 records a comparison of distribution of white counts as recorded by Maxcy in 46 cases, and as noted in 40 counts taken on 24 persons in our series:

TABLE VIII

White Count	Maxcy's Series	Our Series
3,000 to 4,900	3	2
5,000 to 6,900	7	13
7,000 to 8,900	20	14
9,000 to 10,900	6	8
11,000 to 12,900	7	2
13,000 to 14,900	2	1
15,000 and over	1	0

In our series, the average white blood cell count was about 7,500. Two cases had counts below 5,000. The lowest was 4,400 on the fifth day of

illness. Two were above 10,000, the highest being 14,400 on the eighth day of illness. Several counts made on the same patient (11 out of 24 patients had such repeat blood counts) showed a tendency to drop after the first week of illness.

The polymorphonuclear percentage was commonly between 60 and 80. Percentage of polymorphonuclears in 39 differential counts is shown in table 9. A relatively high ratio of polymorphonuclears occurred early, with later shift toward greater percentages of lymphocytes.

Weil-Felix Reaction. The agglutination of Proteus X_{19} with blood serum of patients usually became positive in diagnostic dilution between the tenth and fourteenth days of illness. Nineteen of 29 cases in which the day of illness could be determined quite accurately became positive within this period. Four became positive before this; one on the sixth day of illness; two on the eighth day, and one on the ninth day. A titer of 1:160 usually is stated to be diagnostic. We usually require a minimum titer of 1:320 for a positive diagnosis by a single test. Still more conclusive is a

TABLE IX

40 to 49%	4
50 to 59%	8
60 to 69%	9
70 to 79%	11
80 to 89%	7
Total	39

rising agglutination titer in repeated tests. Nine of our cases had negative tests or positive in 1:20 dilution on the tenth day or before, and later became positive in diagnostic dilutions of 1:160 or over. Cases frequently had positive tests to the highest dilution set up, i.e., 1:2560 or 1:5120.

Two other strains of Proteus organism, X_2 and X_k, the latter known as the Kingsbury strain, were used in Weil-Felix agglutination tests performed on the last three cases. The Kingsbury strain is particularly valuable in differentiating the mite-borne typhuses. In this group, complete agglutinations in higher titers are obtained with the X_k organism and in lower titers with the X_{19} and X_2 strains. Because of the continuous traffic between the Hawaiian Islands and Japan, the possibility of introduction of a mite carrier was considered. The reactions in lower dilutions, with X_2 and X_k strains and reactions in higher titers with X_{19}, obtained in our cases, are in accord with experience elsewhere in rat flea-borne typhus. Human typhus likewise gives complete agglutination in higher titers with Proteus X_{19} than with both X_2 and X_k strains.

Other laboratory tests were done on these cases, with negative results: stool cultures for typhoid, paratyphoid A, B, dysentery, 11 cases; blood Widal, 14 cases; blood culture, 4 cases.

D. Complications

Complications, in addition to pharyngitis, bronchitis, mild pyuria or hematuria, recorded under symptoms or laboratory data were:

Toxic thyroid, one case (probably present before but aggravated by the typhus); pyelitis, one case; secondary anemia, one case; furunculosis, two cases. No mortality occurred in this series, and only one death * has been recorded in the Territory, as due to endemic typhus.

No particular tendency to special complications is noted by any authors except Brill, who noted regular occurrence of bronchitis. Brill, Blatteis, and Maxcy had a few cases of bronchopneumonia and otitis media. Other rare complications, such as phlebitis and suppurative parotitis, occurred, as they may, in association with any febrile illness.

E. Differential Diagnosis

In differential diagnosis, the following conditions most commonly are considered:

(1) Upper respiratory infection of influenza type
(2) Meningitis (lymphocytic chorio-meningitis is particularly to be considered)
(3) Pyelitis
(4) Sepsis
(5) Typhoid fever
(6) Spotted fever or other members of the rickettsial group may be important in other communities.

The majority of the earlier cases were considered as probable influenza, typhoid or other general infection of unusual type. More recently it has become our custom to suspect typhus when several of the following symptoms present themselves during the first week:

(1) Persistent and severe headache not relieved by ordinary antipyretics and/or small doses of codeine
(2) Persistent but irregular fever
(3) Chills or markedly chilly sensations recurring irregularly
(4) Abrupt onset of above symptoms, body aches or pains also occurring early
(5) Irritability, insomnia, night terrors or mild delirium
(6) Absence of positive physical findings
(7) Normal or slight increase of white blood cells
(8) When, in addition to the above findings, a disseminated, fine maculopapular rash,—appearing first on lower chest and upper abdomen and then extending to back, upper arms and thighs,—occurs between the fifth and eighth days of illness, we feel quite certain of our diagnosis.

* One more death has occurred in the Territory of Hawaii since the publication of Board of Health reports for the fiscal year ending July 1, 1938.

The Weil-Felix agglutination test performed on the patient's blood serum becomes positive in diagnostic titer between the tenth and fourteenth days of the disease.

Summary

1. Typhus and the typhus-like diseases (rickettsial diseases) have world-wide distribution.

2. The most practical classification of the diseases distinguishes at least four groups according to insect vector; namely,

(*a*) Human louse-borne typhus (epidemic or Old World typhus)
(*b*) Murine flea-borne typhus (endemic typhus)
(*c*) Mite-borne typhus
(*d*) Tick-borne typhus.

3. Endemic typhus fever is a disease separate and distinct from epidemic typhus fever, having milder symptomatology, different epidemiology and low mortality.

4. Endemic typhus is prevalent in certain sections of the United States, having greatest incidence in Georgia, Alabama and Texas.

5. Endemic typhus is also prevalent in Hawaii.

6. Epidemiological features of endemic typhus in Hawaii are similar to those of the disease as it exists on the mainland of the United States. Outstanding among these are:

(*a*) High incidence in summer and fall months
(*b*) Greater incidence in urban than in rural districts
(*c*) Greatest incidence in young adult age groups
(*d*) Prevalence is greatest among Caucasian whites as compared with other racial groups. (Japanese and Filipinos have particularly low recorded incidence.)

7. The incubation period is seven to fourteen days.

8. A study of 33 cases personally observed showed a clinical picture similar to that described in cases of endemic typhus in the southeastern United States.

9. The onset is usually abrupt, with chills or chilliness, fever, aching body pains, headache and prostration.

10. Headache continues an outstanding symptom throughout the course of the disease.

11. Irritability, insomnia, night terrors or mild delirium are not infrequent.

12. Gastrointestinal symptoms include nausea and vomiting early, anorexia usually throughout the febrile period, constipation frequently, abdominal discomfort, mild diarrhea occasionally.

13. A palpable enlargement of the spleen, reported by some writers, was not found in our series.

14. Mild pharyngitis usually is seen early in the course of the disease.

15. Fever continues about two weeks, oftentimes with irregular fluctuating curve, reaching a height of 103° to 105° by the end of the first week. Fall is most frequently by rapid lysis. The pulse is generally slow in relation to the peaks of fever. Diaphoresis frequently accompanies wider temperature fluctuations.

16. The rash is characteristic, disseminated, maculopapular and appears usually between the fifth and eighth day.

17. White blood cells average 7,500 and polymorphonuclears range between 60 per cent and 80 per cent.

18. The Weil-Felix agglutination test becomes positive in diagnostic dilutions (1:160 or above) usually between the tenth and fourteenth days of the illness (sometimes by the end of the first week).

19. Complications are rare and mortality very low in Hawaii. In the mainland of the United States a maximum mortality is 5 per cent. Most deaths have occurred in persons over 45 years of age.

Conclusions

Endemic typhus fever is a disease of sufficiently frequent occurrence in certain communities to warrant consideration from an epidemiological and clinical viewpoint. Such a situation exists in Hawaii and at least parts of the mainland of the United States. In these sections, endemic typhus fever should be suspected in persons suffering from irregular fever and general toxemic symptoms persisting over a week, particularly when headache is intense and persistent, and when a generalized rash occurs about the end of the first week of illness.

I am indebted to Dr. James R. Enright, Director of the Division of Communicable Diseases, Territorial Board of Health, for assistance in obtaining data in regard to the Epidemiology of Typhus Fever in Hawaii; to Dr. R. E. Dyer for permission to use chart and map illustrating the incidence of endemic typhus fever in the United States; and particularly to Dr. L. F. Badger, Surgeon, United States Public Health Service, for assistance in obtaining materials and for discussing and reviewing my paper during various stages of the study.

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INSIGHT AS AN AIM IN PSYCHOTHERAPY *

By Hervey Cleckley, M.D., *Augusta, Georgia*

An old friend of the writer's who recently visited one of the most celebrated medical clinics in the world, recounts with creditable humor the following incident which occurred during the prolonged and elaborate examination to which he was submitted. The patient, pressed by responsibilities of a busy life, had neglected outdoor games and other exercises for many years and at the time of his admission to the clinic weighed 40 or 50 pounds more than a generous allowance for his height and bony framework would grant as reasonable.

After painstaking and prolonged roentgenologic, serologic, metabolic and directly physical procedures, this man, apprehensive but prepared to face the worst, was stripped to complete nudity and led into a circle of specialists. He took his place somewhat diffidently on the metal-topped stool, visible on all sides to the grave and searching scrutiny of more than a dozen pairs of solemn eyes. Some of the faces were lined with age, some bearded; others, though still young, were no less impersonal or less impressive. All kept focused on him an unremitting attention while various members of the circle commented on his pupillary reactions, his abdominal reflexes, his cardiac sounds and other pertinent points. As the examination proceeded the patient was put at his ease by a disarming smile from one renowned medical scientist, a comment fraught with kindly humor from another. Turning at last to a summary of the diagnostic situation these celebrated specialists piled up negative reports in reassuring unanimity and, responding to the patient's obvious manifestations of relief, relaxed their formality. Suddenly the comments began to bear on the patient's physical aspect as a whole, his height and general outline, the thickness of his panniculus adiposus, the sagging protuberance at his mid-section, the masses of fatty tissue that probably gorged his omentum and all but crowded out his intestines, the vast and unnecessary vascular equipment and cardiac exertion demanded by this impressive outlay of useless blubber. The question of whether a man of such proportions would ever pause to think what effect he might have on his marital partner's esthetic or romantic sensibilities escaped in gentle inuendo. The fact was not spared that this able, robust man, still in his thirties, had become seriously disfigured and all but disabled by the useless loading of fat he had allowed his body to accumulate. In cool scientific appraisal with occasional spicings of unmalicious wit the comments played upon the nude and uncomfortable victim.

The gastro-enterologist, who had become genuinely fond of the patient

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during their many previous meetings for diagnostic procedures, deliberately asked the cardiologist, "How many years has it been since we were privileged with such a sight as this, Doctor?"

"Among the six hundred and forty physicians at our clinic" the cardiologist, shaking his head, drily answered, "few appearing in such Pagan nudity would be confused with Ganymede or with Memnon Son of the Dawn. But among us we have no such man as this."

The comments continued for some time, a tone of amiable banter relieving the situation of any serious impoliteness, but still allowing the patient ample opportunity to contemplate his body image in reflection from this encircling battery of distinguished medical observers.

This incident is not related here for its anecdotal value but because the writer seriously considers it an example of psychotherapy. It has, furthermore, proved to be effective psychotherapy. At the present writing, several weeks since the patient's dismissal from the celebrated clinic, he is 14 pounds lighter, feels stronger, happier, more energetic and in every way *healthier* than he had felt for many years. He had no surgical operations. He was given no medicine at all. The advice to lose weight and instructions about how to lose weight by diet and exercise had often been offered by physicians in the past. This patient had verbally and perfunctorily agreed; but he had nevertheless made no serious effort to change his habits of life. Progressive loss of endurance, vague but persistent cardiac and gastrointestinal symptoms, a diminishing sense of well-being had driven him to fear serious organic illness and in consequence to live in uneasiness and dread. The seriousness of his situation led him to travel nearly 2,000 miles at considerable sacrifice of time and money for examination and treatment at the great medical center. Though this patient got neither medicines nor operations the writer maintains that his pilgrimage was not made in vain.

What did the patient receive that convinces us his money and time were well-spent? The answer is very simple. He got insight. This new knowledge of himself which we choose to call insight consisted in this case of a real awareness: (1) Of his body as it appeared to others, (2) of the physical and physiological handicaps of a body all but overwhelmed with excess fat, (3) that his body could be relieved of this burden by simple measures demanding reasonable persistence but no very great effort or deprivation on his part. It is perhaps not too much to say that this patient's resistance to a real and conscious awareness of his body-image, an awareness in the sense of Schilder's formulations,[1] was overcome and, seeing himself from this aspect as he really was, he at once set about changing his body. With these changes the body became not only more healthy and effective but, more acceptable to himself as well, even a source of pride and satisfaction in that composite of self-awareness or consciousness in which we all experience life as psychobiologically integrated entities or personalities.[2, 3]

Whatever school of psychotherapy one may favor and whatever type of presenting symptoms one may have to deal with, no aim is more funda-

mental than the aim of helping the patient gain insight. Nor is any aim more ambitious. The case cited above is hardly one that would be regarded by most physicians as a psychiatric problem at all. The patient, an intelligent and apparently a well-adjusted person, was, of course, free from any sign of a psychosis. There were no discernible physical or personality symptoms that even a very imaginative psychiatrist could say were directly psychogenic in the ordinary sense. Yet it cannot be denied that the one significant factor in his rapid progress towards regaining vigorous health is his gain in insight. One might object and say that the real factors are his changed dietary habits and his new program of recreation and exercise. These, however, are plainly secondary. They had as a matter of fact, been prescribed often in the past. The patient himself freely admitted their advisability. Yet he did not adopt them. And the only possible reason why he did not adopt them is because he did not really see or feel with emotional conviction their desirability and their importance. Or, we might say, he did not feel this sufficiently.

Laymen and even physicians uninterested in psychotherapy might insist that it is strange, or even preposterous, to maintain that a patient of good intelligence is unable to appreciate the necessity of such measures as dieting and exercise in the case just mentioned. Such skepticism, however, does not invalidate the simple fact that this patient did not appreciate this necessity and that the failure to appreciate it, in any sense that has real meaning, is proved by his failure to do anything about it.

To physicians interested in psychotherapy this astonishing inability of normal and even of extremely intelligent persons to see obvious factors in their life situation is as familiar as the morning sunlight. The child who is a feeding problem often enough has a mother who nags at him through every meal, cajoling, teasing, threatening and often losing her temper in frantic attempts to make him eat. The most subtle dialectic and the most impressive citations only too frequently fail to persuade such a mother to leave her child alone at meal times even for a day. The physician assures her that the child's failure to eat is because he is so harassed and overpersuaded that the food loses its savor. The mother often agrees with the physician but continues in her activity. The patient who consults a dozen different physicians each year vainly seeking a cure for constipation which has made his life a misery for twenty years will usually be deaf to all explanations that the many and powerful laxatives with which he alternately scourges and paralyzes his bowel functions are a very important factor in the causation of his disorder. The neurotic drinker who loses his digestive powers, many excellent positions in business, his standing in the community and most of the pleasures of life is not easy to convince that the excessive drinking, which usually has ceased to give him any of the satisfaction which ordinary social drinking gives, is itself a very important factor in causing the situation which he vainly seeks to escape by drugging himself with drink. This neurotic drinker will often agree verbally, and will think that he really

agrees, but he does not see in the sense of seeing with emotional conviction, and so he does not actually agree. If he did see and agree he would stop drinking. The old adage that one should judge a person's intentions or convictions by his actions rather than by his words is theoretically understood even by middle grade morons * but in practice many scholars and scientists of high repute show no grasp of its meaning.

Insight into such problems as those mentioned is not easy for the patient, however great his intelligence, in any true or useful sense. In the more readily apparent psychiatric problems manifested in the classical psychoses and psychoneuroses a loss of insight is more obvious.

In psychasthenia, for instance, a vivid and persistent fear of contamination may cripple the patient's life, making it all but impossible for him to open doors without first wrapping the doorknobs in sterilized cloths, causing him to shrink in genuine disgust from the touch of a lovely woman's hand since he realizes that her hand may have touched a fence post that had been touched by someone else who had shaken hands with a person who, in turn, had been in contact with someone suffering from an infectious disease. It does little good to assure such a psychasthenic patient that there is no appreciable danger of catching this particular infectious disease even by direct contact with the sufferer, or to point out that the causative microörganisms normally dwell in the psychasthenic's own body and in the bodies of other people physically sound. The psychasthenic often knows all this. He is aware that his fears are not grounded in reason. Nevertheless his fears torment him; and if he tries to ignore them he is overcome with disabling anxiety.

In such cases it is not always easy for the physician to discover what is really causing the patient's fear and how his life-pattern came to be constructed in such a fashion. Is it a fear of sexual or aggressive tendencies in the patient, unrecognized by himself and inconsistent with his conscious ethical standards? Did the exaggerated fear of masturbation or ideas of moral uncleanliness born of silly parental ideologies drive him in compensation to symbolize thus his struggle for a hypothetical purity? Can the fear of contamination be traced back to a simple beginning where over-severe and nervous parents demanded too much of the patient as a child in training him to control his excretory functions? Did he as a result of his meet his next problem feeling that he must strive to exceed his actual abilities and sense himself doomed to failure? Did he gradually become overscrupulous in all things under the continuous effort to avoid failure (and especially contamination or dirtiness) by exaggerated procedures? Could the cumulative experiences of life have so shaped him that he must as he stands, almost mechanically and whether he chooses to or not, always struggle, even by fantastic compulsive rituals, to avoid dirt and infection or what is symbolized for him by them?

* This question is placed in the ten year group in the Binet Stanford Psychometric test and is answered correctly by the average child of 10 years.[4]

Even if the physician is able to see the background of such a patient's symptoms the patient himself cannot be made to gain real insight into this whole life scheme by a statement from the physician explaining it. In such cases many months of treatment are often necessary; months during which the physician, whether by the free association methods of classical psychoanalysis,[5, 6] the more direct approach of distributive analysis and synthesis,[7] of individual psychology,[8] or by some other approach seeks to lead the patient to understand his symptoms and what lies behind them. To understand this he must understand himself better, must see and admit motivations that he has not been aware of or admitted to himself; or if one prefers so to state it, which he has not fully appreciated.

Why is it so difficult for patients who suffer with psychoneurotic symptoms to gain this insight? The naive conception of an intelligent person, and many psychoneurotic patients are far above the average in intelligence, takes for granted that he can see ordinary facts when they are carefully demonstrated to him and that, seeing them, he will act on them to his best interests. To demonstrate the fallacy of this conception we need not leave the realm of ordinary life.[9, 10] Everyone has known what it is to reason with a person who we say has a strong prejudice. Whether this prejudice lies in theology, politics, literature or the fashions in women's clothes, we find it uniformly difficult to modify by ordinary reasoning.[11] We also find that the person is unaware of having a prejudice and that he cannot be made to admit our accusation. Indeed as the argument progresses, if we have much capacity for insight, we may begin to wonder who has the prejudice, ourselves or the other fellow. For the purpose of our illustration it matters little with whom the prejudice lies or whether both have prejudices which conflict. To make this point more emphatic one need only mention the various religious sects and political parties with their strongly contrasting beliefs and the intelligent persons in all of them who cannot understand their neighbors' beliefs in contrary doctrines. Or one might imagine a discussion of art between an ardent surrealist and a typical member of the British Royal Academy.[12]

What we know as a prejudice maintains itself against ordinary argument and demonstration which fall off like water on a duck's back [9] leaving it undisturbed if not actually strengthened by its successful resistance.

Why does the prejudice maintain itself so stubbornly? Perhaps if we consider the miser, a familiar character in any community * some simple reasons may become apparent. The miser often has ten times as much money as he could use, even if he should change his ways and live extravagently; yet he goes threadbare, lives in a wretched environment, denies his children ordinary privileges and sometimes even restricts his diet beneath the requirements of adequate maintenance. But what logician can convince him of the absurdity in his life scheme? Who can make him see that he has

* For a convincing and detailed picture of the miser's personality picture the reader is referred to George Eliot's *Silas Marner* and to Arnold Bennett's *Riceyman Steps.*

no need to hoard more money which he will never use? If such a suggestion is made he is likely to explode in wrath. Even if he consents to discuss the question he will use elaborate casuistry which the observer recognizes as being designed (unconsciously) to maintain the miser's own convictions in the necessity of hoarding. However ingenious this casuistry may be it does not convince anyone but the miser. Of course it is he himself whom this casuistry is designed to convince.

A few simple and superficial reasons why the miser cannot see his folly are perhaps obvious: (1) He has invested years of effort and has suffered much in deprivation to fulfill his unhealthy scheme of life. If he should realize its uselessness he would have to see that he had wasted all this effort and suffering. No one cares to see a heavy investment become worthless. A fundamental biological factor, the tendency to avoid pain or hurt, stands behind his protective blindness. (2) He would have to admit that he had for years been a miser, that he had been wrong thousands of times when he so confidently believed and proclaimed himself right. It is distressing to lose face,[13] and to see oneself as having been entirely silly where one thought oneself particularly wise, to face the fact that a major source of pride has been a persistent folly. (3) He would have to change all his habits. Habits are notoriously hard to change and any changing is most uncomfortable. (4) The ordinary pleasures of life have usually lost their appeal since he has denied himself for so long that he cannot imagine immediately what delight they give others. They seem obvious to others as an influence to make him give up his miserliness, but to him they are, so long as he remains a miser, invisible and, so, non-existent. (5) He has, through his long practice of miserliness, come to find a kind of pleasure in self-denial, as well as in hoarding. This pleasure is very real though difficult for the ordinary man to understand. One need only cite such examples as the flagellants [14] who choose to have themselves scourged, the Hindu Fakirs who sit for years on seats of sharp nails, or the sexual masochists [15, 16] who delight in being spat upon, betrayed and otherwise humiliated no less than in being physically beaten by their love objects, to illustrate how readily man can learn to love what is commonly regarded as distressing.

There are reasons then why the prejudice is maintained against the appeals of logic. There are also reasons why the psychoneurotic patient and even the psychotic patient fail to gain the insight which is so important for them to become well. The reasons are often similar. The psychoneurotic patient also dreads to lose face. He may be gaining an unnatural and morbid sort of pleasure from his illness. To see his life-scheme and his hitherto unperceived motivations would cost him pain, shame and great inconvenience. He also has frequently lost the ability to understand the satisfactions of healthy life.

Sherrington,[17] in speaking of organic neurological disorders, has said, " Again in life's final struggle the chemical delicacy of the brain-net can make

distress lapse early because with the brain's disintegration the mind fades early—a rough world's mercy toward its dearest possession." In such situations as that of the miser or the psychasthenic patient we cannot yet detect organic or biochemical changes in the brain. Even if such changes should some day be discerned and measured it would be difficult to prove they arose otherwise than as a result of a certain way of living. In these conditions which we may for the present call psychogenic one sees the same broad biological principle, a mercy towards self, which Sherrington points out in actual brain damage. Such mercy, like euthanasia, we must agree is good when destruction is inevitable. It is, however, inopportune and even tragic if this loss of insight prevails in remediable situations. For then it is loss of insight itself which becomes the physician's most serious problem. To the somewhat imposing question of why an intelligent person should lose the very capacity which would enable him to solve his problems, one might then be justified in answering that it is lost through an untimely and a too ready use of a capacity as intrinsically biological as respiration or the vomiting reflex. Vomiting itself, a most useful mechanism for the preservation of the organism, may become its means of destruction by depleting the body chlorides in remediable situations.[18, 19, 20] And may not one properly add here that the human organism has for its defense many useful mechanisms, conscious and unconscious, which under certain conditions escape voluntary control, or their own status in the involuntary organization, and, blindly overdoing their originally useful function, destroy what they were designed to serve. What is more essential to healthy living than courage? Yet has not blind courage led dogs into fatal encounters with porcupines and numberless Don Quixotes uselessly into the arms of inoffensive windmills?

Insight has been stressed as the factor of primary importance in psychotherapy and the writer believes that this importance can scarcely be exaggerated. It is at insight that the psychiatric illness must strike in order to exist and to maintain itself. Insight is, however, often difficult to gain. Sometimes it cannot be gained no matter what psychotherapeutic efforts are exerted. It is not difficult to see that the process of gaining insight is usually for the time being extremely unpleasant. So too is the lancing of a boil. If insight should come too suddenly some psychoneurotic patients might be overwhelmed with their situation and attempt suicide or suffer the personality dissolution known as a psychosis. In the plainly somatic branch of medicine, surgery, over zealous and peremptory efforts to eradicate a focus of infection may cause fatal septicemia. If, for instance, the psychasthenic patient who avoids contamination so scrupulously, should suddenly realize that it is not really dirt he fears but homosexual tendencies of which he has been unaware, the stress of facing his situation might be disastrous. In cases of serious psychoneurotic illness, therefore, the patient should acquire insight gradually as he gains enjoyment in the ordinary exercises of life, as he finds activities in which he can lose himself and accomplishment in

which he can take pride. It may be necessary for him to build positively some edifice for his personality before he can abandon the old dwelling of his illness.

Often the psychoneurosis, like the miser's way of living, has so restricted the patient's existence that he has, one might say, nothing else to fall back on. It is therefore important to persuade the patient to change his habits, to enlarge his scope of activities, to break the pattern of his unhappy existence as soon as possible. Even the simplest expedients are often useful. A regular hour for going to bed and for arising, simple calisthenic exercises before breakfast, a carefully selected program of reading, definite social activities at stated times, a walk each evening in the sunset during which the patient tries to keep his attention entirely on what he sees and hears about him, plans for each night in the week which must be carried out whatever his inclinations: such a new routine is often valuable in breaking the old pattern of life in which the psychoneurosis flourishes and may help the patient find himself naturally in existence with others as he works to understand himself.

If the patient can be induced to start normal living in even one obscure corner of his map of life the biological tendencies that make for health may find a foothold. The patient will often object to any planned activity giving many elaborate reasons why he cannot adopt each suggestion. He must be persuaded to go on blindly with new activities whether or not they seem, for the time being, pleasant or helpful. Mere logic, however invulnerable it may be, will seldom induce the patient to follow the physician's advice. What then will induce the patient to do so? There is perhaps no way in which an answer can be given briefly. The degree of the physician's real understanding of the patient, the intensity of the physician's interest in the patient as a human being, everything that the physician has felt and enjoyed and suffered in life and living, no less than the physician's measurable technical knowledge, will influence this issue.[21]

Psychotherapy is often difficult and many of its problems call for considerable patience, wide experience, systematic training and a type of concern with people as personalities which cannot readily be taught. It is nevertheless true that the physician in general practice often overlooks simple opportunities to help patients with psychiatric problems.[22] Sometimes only a little time and effort are needed to bring about real improvement in the patient's health and happiness. An interest in personality problems is the most important factor in enabling the general practitioner to seize these opportunities and to make himself more useful to his patients.

Summary and Conclusions

1. Psychotherapy has often been regarded by other branches of medicine as an isolated if not a metaphysical or even an occult and unworthy art. It is here maintained that such differences arise from limitations of viewpoint.

The fundamental biological strivings, whether the organism is confronted with a painful furuncle or with an errant bride, have something in common.

2. Even the most obviously somatic medical problems often have a readily demonstrable personality factor; and this factor is sometimes fundamental.

3. The loss of insight, which in some degree accompanies all personality disorders, is the fundamental problem in therapy. This loss is not always replaceable but efforts directed toward improving insight are the primary and logical aim of a reasonable psychotherapy.

4. Biologically there is nothing more abstruse or mystical in this aim than in the surgeon's aim of aligning the angulated bone fragments in a comminuted fracture. Practically the problem is often more difficult. This degree of difficulty may be at times discouraging but should not be an excuse for losing interest.

5. The misunderstanding and even the mistrust of psychiatric methods by the average physician has for years been recognized. The psychiatrists, with their formidable terminologies, their elaborate and sometimes conflicting ideologies, are perhaps responsible, in part at least, for this misunderstanding and mistrust. The importance of expressing psychiatric aims in terms consistent with ordinary medical thinking has been recently emphasized.[23, 24] This presentation of homely personality problems in simple terms is intended as a small effort in affirmation of psychiatry's unity with medicine in general.

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CASE REPORTS

HERNIA OF THE DIAPHRAGM; REPORT OF TWO CASES*

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ALTHOUGH an increased number of cases of hernia of the diaphragm is being recorded, it may be still regarded as a rare condition. A great number of types and varieties and degrees of hernia have been recognized and various attempts at classification have been made, based on anatomy, embryology, etiology, and contents, but it is impossible to distinguish these clinically. Perhaps the most satisfactory method is to consider these all as (1) traumatic or (2) non-traumatic. The traumatic may be divided into (*A*) indirect, injury resulting from a crushing blow to the chest or abdomen; (*B*) direct, the result of the formation of a window of the diaphragm following stabbing or shooting. The non-traumatic may be (*a*) congenital deficiency or (*b*) acquired after birth.

Hedblom [1] in 1932 mentioned between 1400 and 1500 reported cases of various types and added 600 from his own records. Since then, Stobie [2] has reported five cases, Marks,[3] 29 cases, Harrington and Kirklin [4] from the Mayo Clinic, 241 cases including 131 operated upon between 1900 and 1937. Root and Pritchett [5] reported 31 cases from the Cleveland Clinic and Trusdale [6] reported 303 cases in children including 13 of his own operative cases. More recently, Bowen [7] has given a good summary of the recent literature and has summarized the facts regarding incidence, symptoms, physical signs, diagnosis, prognosis, classification, treatment, and technic of operation, largely based on the above mentioned reports. These phases are too lengthy to discuss in this paper.

There is considerable variety in the reported frequency of this condition. At the Mayo Clinic, it is estimated that diaphragmatic hernia occurred once in about every 18,000 roentgen-ray examinations. Only two cases were found in the Guys Hospital in London from 1856–1920, and MacMillan reported three cases in 15,000 examinations in the United States General Hospital No. 8. In the Waterbury Hospital,[8] only six cases have been recognized in the past six years out of about 24,000 roentgen-ray examinations, about one a year or one every 4,000 cases.

To some extent this variation is due to the definition of what is considered true hernia. Some do not include the minor forms of esophageal shortening and hiatus hernia.

The following two cases have seemed to be sufficiently unusual and interesting to be worth recording in detail, especially as it was possible to secure an artistic record of the first case.

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From the Medical Service of The Waterbury Hospital.

CASE 1

Mrs. L. C. S. was 54 years of age when she first consulted me in 1931 complaining of headaches and of some nervous troubles. She gave a history of having had typhoid fever, "typhoid pneumonia," and the exanthemata as a child, and curvature of the spine since childhood. She had a fracture of the right hip at the age of 42 and pneumonia at 52.

In 1923, following a series of attacks of upper abdominal pain off and on for five or six years, which had been relieved only by morphine hypodermically, she had a cholecystectomy and appendectomy. She apparently developed bronchopneumonia postoperatively. Notes from the hospital record give no details of the operative findings. The pathological report, however, showed a chronic, fibrotic, obliterative appendicitis and a gall-bladder measuring 6.5 cm. in length which grossly and microscopically showed no evidence of inflammation.

She had had frequent severe headaches which she felt were related to her digestion, or her "liver," occurring at 4 or 5 o'clock in the morning, and not related to eyestrain. She had frequent colds with sore throats and had considerable mucus in her throat but no actual tonsillitis. There was no allergic history. In her cardiorespiratory past history she had complained of moderate dyspnea on exertion for years. She had a chronic cough and was very susceptible to bronchial colds. She had occasional edema of her ankles.

She had a fair appetite but was a small eater. She was troubled with gas and some gulping or regurgitation of food after meals, and at times had a feeling of constriction and of fullness in the abdomen. Her bowels moved regularly although she occasionally took "liver pills" for gas. She had nocturia once or twice most of the time, occasionally some frequency and dysuria with her colds. Her menses began at 12 and were apparently normal. She was married at the age of 30 but was never pregnant. Menopause occurred at 45.

She had been stoop-shouldered from a curvature of the spine since childhood, but no further details were known. Her weight stayed around 110 to 115 pounds.

Physical examination showed a rather remarkably deformed, slightly-built adult woman with an upper dorsal kyphosis and left lateral scoliosis resulting in her left shoulder being higher than the right, and constricting her chest laterally. This brought her costal margin almost to the iliac crest. She was quite agile, cheerful, friendly and coöperative. Her eyes, ears, and nose were normal; her tonsils were enlarged and boggy. Her soft palate and uvula were swollen most of the time. Examination of her chest was unsatisfactory because of the deformity and asymmetry. Her heart seemed moderately displaced to the right but the sounds were normal. Her blood pressure ranged from 165 mm. Hg systolic and 95 diastolic and 170 systolic and 110 diastolic to 120 systolic and 95 diastolic at various times. There was very little expansion of her chest wall and with the rigidity and curvature of the spine, the distant breath sounds on the left were not thought abnormal, as there seemed to be no definite dullness on percussion. She almost constantly showed fairly numerous, moist râles in her right upper chest, front and back, with occasional pleural friction sounds. Her abdomen was much shortened, the liver was enlarged but with her deformity that did not seem particularly abnormal.

In 1934, she was sick for about four weeks with bronchopneumonia, following which she complained of pains in her abdomen with some regurgitation of food after eating. A mass of about 8 by 10 cm. was found in her left mid-abdomen which did not seem to be connected to the pelvic organs or related to her renal or intestinal tract. She was admitted to the Waterbury Hospital March 5, 1934 for observation and gastrointestinal study with question of intestinal obstruction. Her temperature, pulse and respiration were normal. Hemoglobin was 98 per cent; erythrocytes 4,700,000; leukocytes 5,000; polymorphonuclears 64 per cent; monocytes 8; lympho-

cytes 26; endothelials 2; blood Wassermann test was negative. The gastrointestinal roentgen-ray report of March 5, 1934, was as follows:

The fluoroscopic examination showed gross pathologic findings in the left chest. The barium solution passed down the esophagus to the usual position at the cardiac end of the stomach. (Figures 1, 2, and 3.) From this point, it passed directly up-

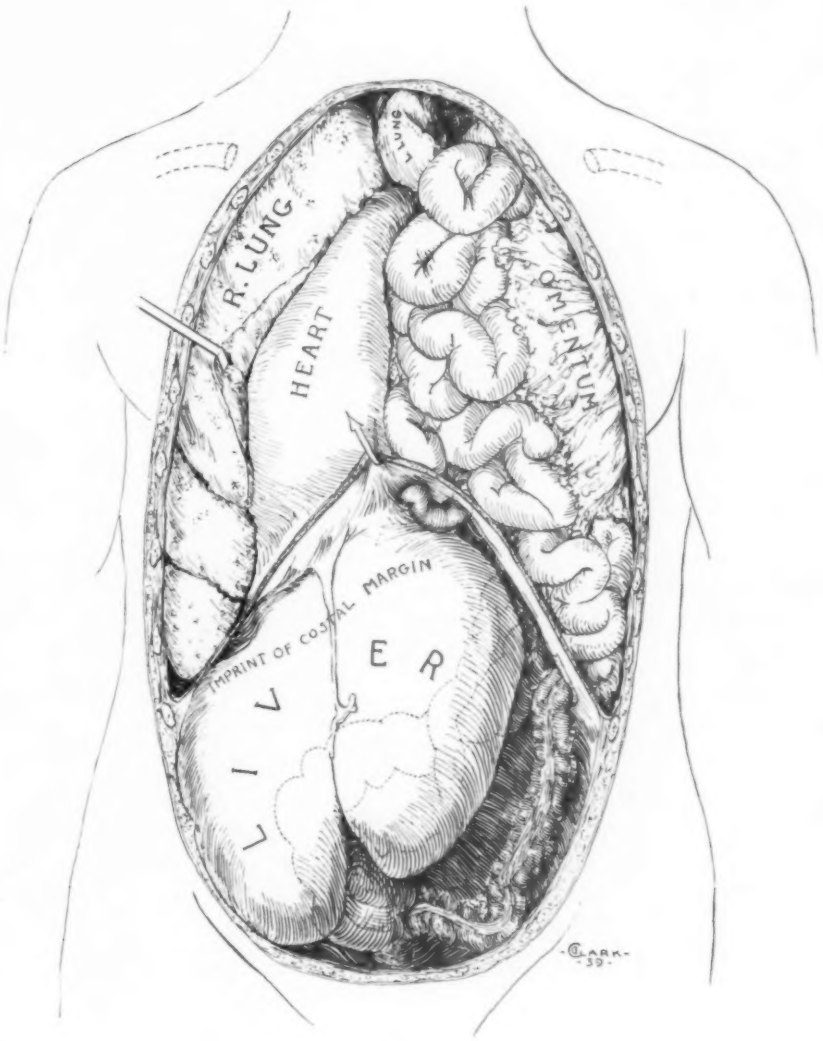

FIG. 1.

ward to within two inches of the clavicle, then forward and downward. The duodenal cap was seen only in lateral view. A gas bubble was in the stomach, within 1 cm. of the level of the clavicle. Above this was a tissue shadow which was probably part of the diaphragm. There was a small amount of barium in the stomach at the end of six hours and a large amount of barium in the small intestines, lying in the left chest. The head of the meal had reached the cecum which lay in the midline of

the pelvis. At 24 hours, about half of the barium was evacuated. No roentgen-ray connection could be made out of involvement of the mass in the abdomen with the small or large intestines.

Diagnosis: Eventration left half of diaphragm.

She was seen by two of the surgical staff in consultation at the time. It was agreed that she was a poor surgical risk and that the abdominal mass was probably

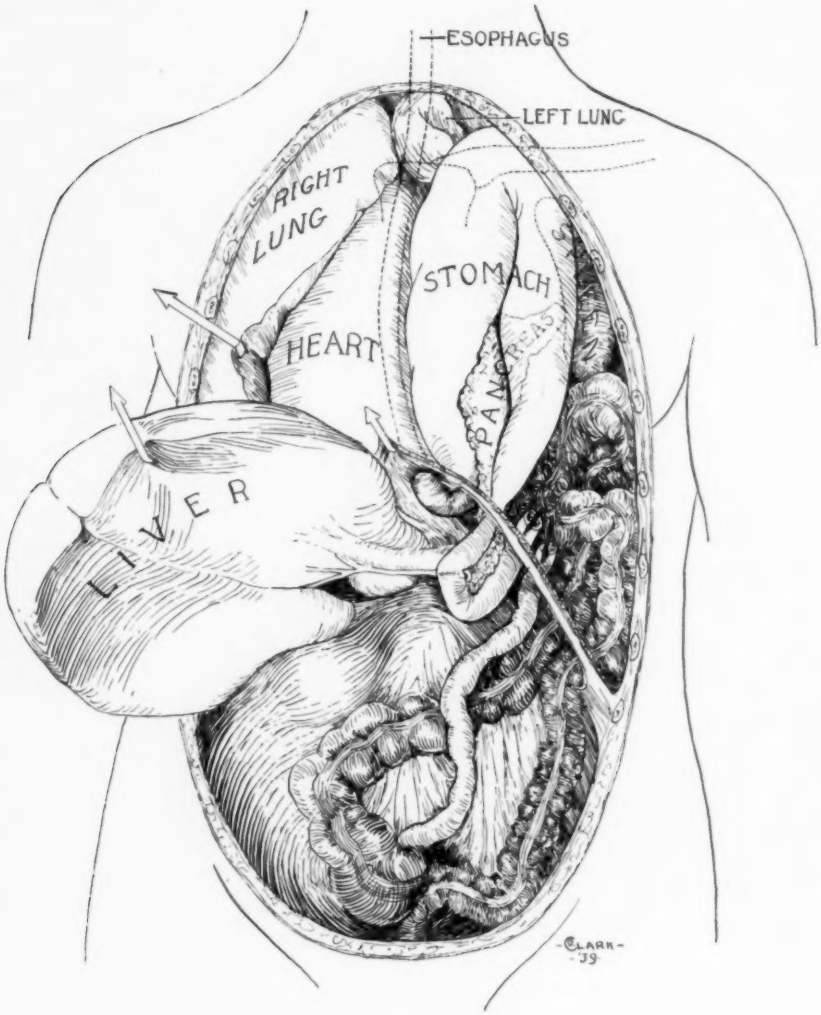

FIG. 2.

a cyst of the mesentery. With a bland diet and small doses of barbiturates her symptoms subsided. She was seen off and on during the subsequent three years for a variety of minor complaints, but in general, her health was not as good as in previous years. She had increasing dyspnea on exertion, edema of her ankles, and some cystitis and pyelitis. Her vision was disturbed by some vitreous opacities. The mass in her abdomen seemed to be getting larger. In 1937, after an episode of

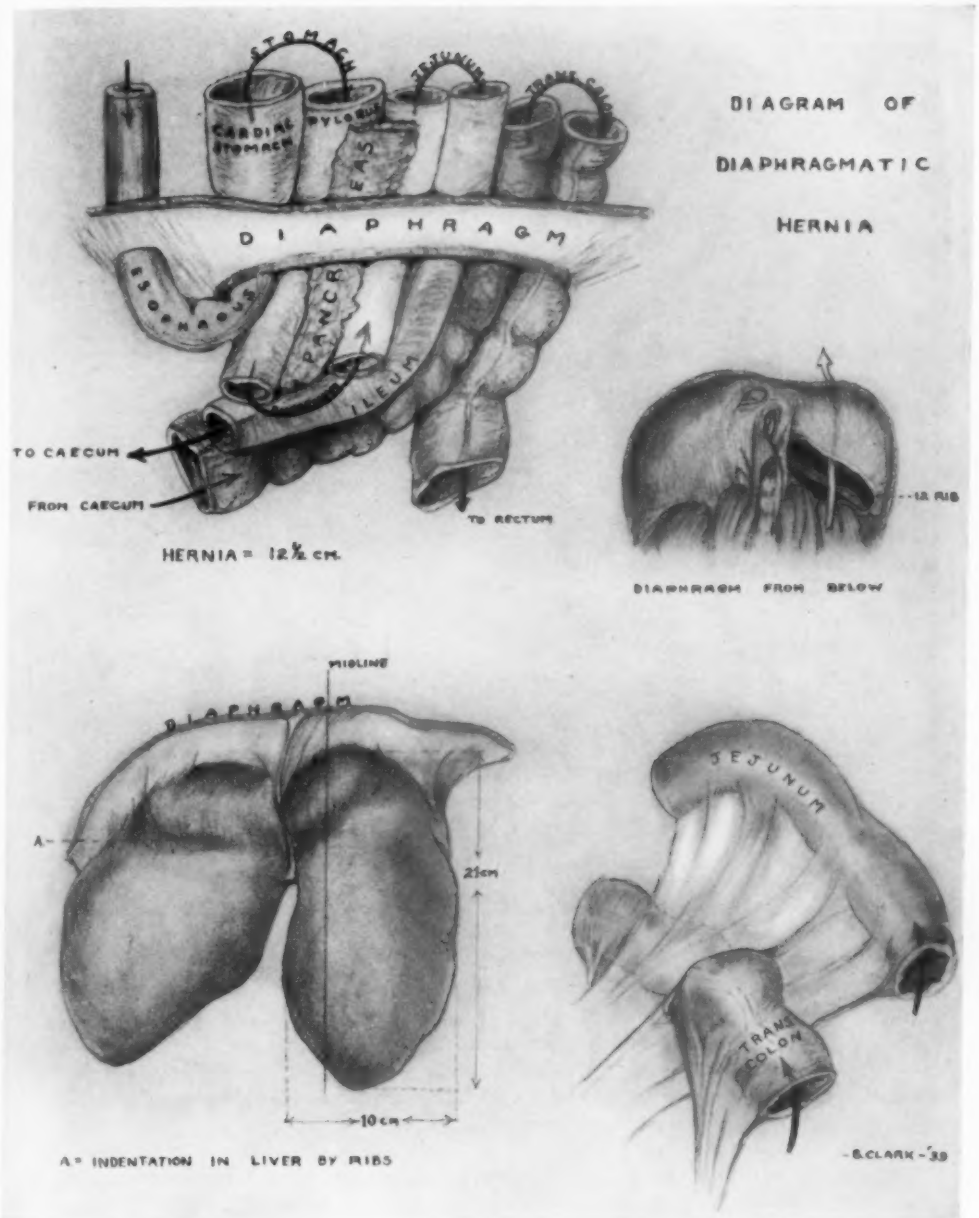

FIG. 3.

cystitis, a pyelogram (figure 4) was taken which showed the kidneys, ureters and bladder to be normal and to have no connection with the abdominal tumor. She seemed to improve after that, and was quite active. She took several long automobile trips in the summer of 1937 and spent several weeks in Florida the following winter. During October and November, 1938, she had more severe headaches, was

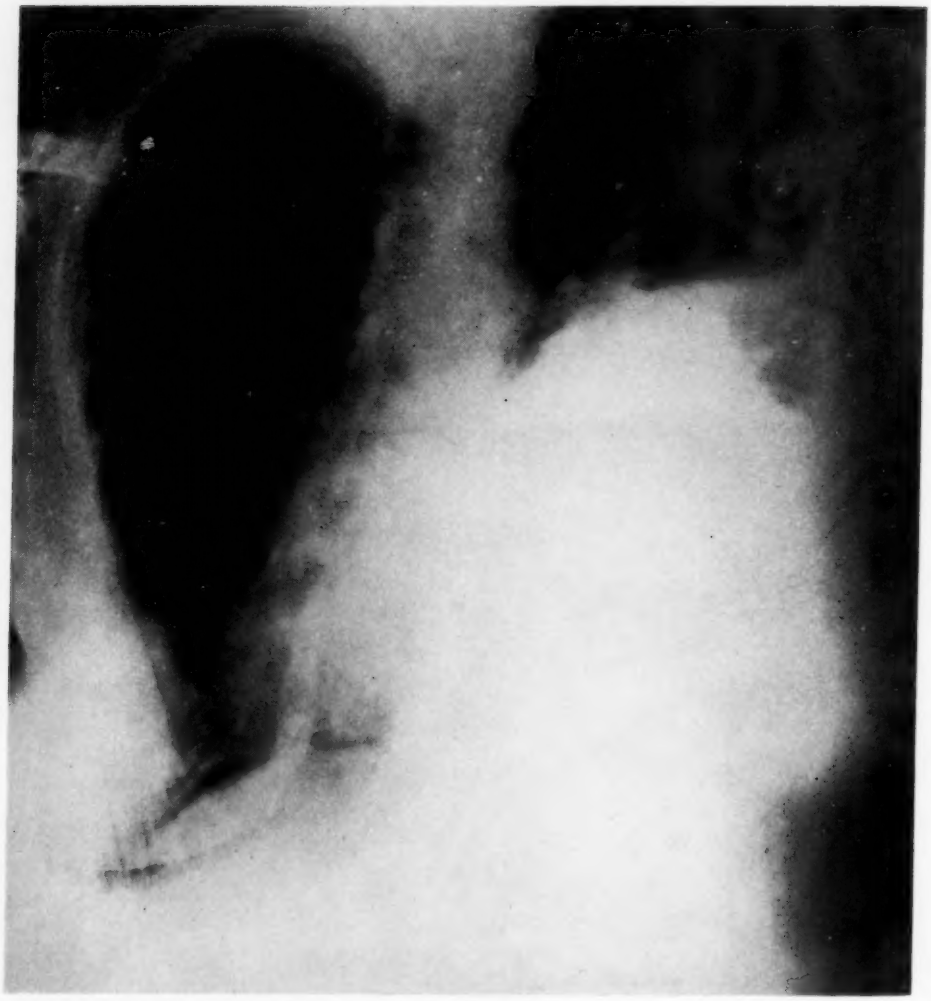

FIG. 4. Chest roentgen-ray showing barium meal in the stomach within the left thorax. The gas bubble is almost on the level of the clavicle.

weaker and more dyspneic. The week before Christmas, she developed a cold and a deep cough. She became much weaker, and died suddenly in her sleep Christmas afternoon, apparently a cardiac death.

Permission for an autopsy was granted and performed through the courtesy of the undertaker about 18 hours after death and after embalming, with the findings as follows:

The body was that of a white adult female apparently about 60 years of age. The body was well-developed and well-nourished; the head and neck were not remarkable. The thorax was deformed by a posterior curvature of the thoracic vertebrae with some left lateral scoliosis. There was a lateral compression of the thorax which greatly increased the anterior and posterior diameter of her chest. The costal margin reached nearly to the iliac crest. There was a mid-line operative scar from the umbilicus to the symphysis.

The body was opened by mid-line incision and the breast plate removed to expose the thorax. A remarkable picture (figure 1) was presented. The left thoracic cavity appeared entirely filled with coils of small intestines, all lying above the diaphragm. No lung was visible on the left side. The pericardial sac was suspended about perpendicularly, lying to the right of the mid-line. The right lung was compressed by the pericardium. Below the diaphragm, the entire abdominal cavity was filled by the liver which was flattened and bilobed, extending to within two inches of the symphysis pubis. The mass felt during life was the large left lobe of the liver. The heart was about normal in size. There were no pericardial adhesions. The valves and endocardium were smooth and glistening and normal in appearance. The coronary arteries seemed normal and there was no special sclerosis.

The left lung was not visible on inspection but was found lying high up in the left apex, almost completely hypoplastic, not over six or seven cm. in any dimension, white in color. There was very little anthracosis. The cut section was spongy and normal in appearance. The right lung was dark in color and was completely adherent to the thoracic wall throughout. There was considerable anthracosis but no gross scarring. The cut section showed congestion at the base. The diaphragm seemed normal on the right, but on the left there was an opening along the posterior half, 12 to 13 cm. in length and about 2 to 3 cm. in width. The margin of the opening was smooth, hard, and rounded, and the cut section showed a well-developed muscle band with fibrosis. The anterior half of the left diaphragm was normal.

The esophagus was lying in the posterior mediastinum and passed normally through the diaphragm. (Figure 2.) At a point about two cm. to the left, the cardiac end of the stomach appeared through the hernia. It passed upward and backward to the level of the clavicle where at its greater curvature, it passed forward and downward, about normal in size and shape, to the pylorus which joined the duodenum just above the level of the diaphragm. The stomach was full of partially digested chyme. The duodenum could be traced downward through the opening in the diaphragm. The ampulla of Vater was located and the bile duct found passing up to the hilus of the liver. The jejunum then passed upward and was lying in the anterior left thoracic cavity. The ileum was traced back downward through the hernia. The terminal 18 inches passed downward across the posterior abdominal wall under the liver to the right iliac fossa where it joined the cecum in its normal position. The appendix was not found. The cecum was dilated but otherwise was normal. The ascending colon passed upward, parallel to the ileum through the opening in the diaphragm. The transverse colon was found lying within the left thorax. The omentum was also all above the diaphragm, lying against the left axillary wall. The descending colon passed downward along the left posterior abdominal wall directly to the rectum.

The pancreas was lying partly in the hernia, parallel to the stomach in about the center of the thorax. It appeared normal and was of the usual consistency.

The spleen was larger than normal, about 15 by 6.5 cm. It was dark and congested and was lying in the left posterior upper thorax, almost under the scapula. It had the appearance of chronic passive congestion.

The liver was deformed, flattened by the pressure of the costal margin against the lumbar lordosis into two lobes of about equal size, appearing as a pair of saddle bags, occupying the whole abdominal area. Each lobe was about 10 cm. wide by about 20 cm. in length and from 3 to 5 cm. in thickness. The cut surface appeared normal except for heavy strands of fibrosis through the hilum. A small quadrate lobe was present; the gall-bladder was absent.

The kidneys were in the usual position. They were smaller than average, the right measuring 10.5 by 6.5 cm., the left, 9.5 by 4.5 cm. They were rather lobulated. The uterus was atrophic. Small, hard glands were present in the pelvis but otherwise

no abnormal structures were noted. The spine was shaped like a question mark or shepherd's crook but did not appear grossly abnormal except in the region of the lower lumbar vertebrae where it seemed to be thickened. The spine seemed absolutely rigid. Sections were taken from the different organs but microscopic examination was essentially negative, except for some generalized arteriosclerosis and congestion of the right lung. Diagnosis was:

1. Arteriosclerotic heart disease
2. Bronchopneumonia
3. Hernia of the diaphragm (congenital)
4. Kyphosis and scoliosis of the spine.

Discussion

The deformity of her skeletal structure from childhood, the almost complete transference of her abdominal viscera into the left thorax without any history of acute symptoms, the under-developed condition of her left lung, and the fibrous margin of the diaphragm all point to a congenital etiology of her condition. It is of interest that with such an abnormal arrangement of her organs, she survived (1) typhoid fever as a child; (2) bronchopneumonia at least three times during her life; (3) a fracture of her hip at 40; (4) a cholecystectomy and appendectomy at 45, and lived to be nearly 60 years of age. Although never very robust, she thoroughly enjoyed life.

The surgeon at the time of her operation did not suspect anything abnormal in the position of her organs, the gall-bladder and the appendix being in about the expected positions. From the pathological report of the gall-bladder and appendix, it is possible that the symptoms she had had at that time may have been related to the hernia. However, she apparently had fewer attacks after the operation. There evidently had been considerable enlargement of the liver during recent years.

Although the roentgen-ray diagnosis was that of eventration of the diaphragm, the actual condition was hernia. Eventration is that condition in which one leaf of the diaphragm is weakened or paralyzed and is pushed upward, very much thinned, compressing the lung, but always keeping the abdominal and thoracic viscera separated. Hernia, as in this case, is a condition where an opening in the diaphragm permits the abdominal contents to be extruded into the thorax within the pleural cavity and in direct contact with the mediastinum and lung.

Case 2

Another case of almost equal interest and presenting some unusual problems of diagnosis and therapy was a 15 year old Italian boy who was brought into the Waterbury Hospital by ambulance, February 11, 1937. The story obtained from the attending physician was that the boy had returned from school the day before, complaining of a pain in the abdomen. In spite of this, he ate a large supper. Later in the evening, he began to vomit and this continued throughout the night. The boy was given pantopon grains ⅓ about 9 p.m., at which time physical examination seemed to be negative. At 8:30 in the morning, the visiting nurse gave him two enemas which returned clear. The temperature was 99.8° F. The doctor saw him again at 3:30 p.m. and immediately sent him to the hospital by ambulance.

At the time of admission, the boy was extremely cyanotic, dyspneic, and complained of severe pain in the upper right chest. He was gasping for breath, respirations were 46, pulse was 120, and temperature was 103°. Blood pressure could not be

FIG. 5. Chest roentgen-ray six hours after the barium meal which is still mostly in the thorax.

determined. Hasty examination of the chest revealed what was thought to be complete consolidation of the whole left lung and the lower right chest. While being examined, the boy went into convulsions and died, 25 minutes after admission.

Portable roentgen-ray of the chest which was taken on admission to the hospital was rather unsatisfactory. It showed the right costophrenic angle in its usual position and the heart displaced out of the left chest. An area of pneumothorax, approximately 10 cm. in diameter, was seen in the upper part of the left chest. Below this was a mottling suggestive of fecal material. The patient died before the examination could be repeated. Diagnosis was left pneumothorax.

The leukocyte count showed 24,300 per cm., 87 per cent neutrophiles, 7 small lymphocytes, 1 large lymphocyte, and 5 mononuclears.

FIG. 6. Abdominal film taken six hours after barium meal with the head of the meal in the ascending colon, also showing the old fracture of the neck of the right femur.

The autopsy, performed 20 hours post mortem and after embalming, showed a well-developed and nourished young adult male, with no abnormal external features. A mid-line incision was made and the breast plate removed to expose the thorax. The stomach and part of the transverse colon were found resting in the left pleural space. The left thorax also contained considerable quantities of gas under pressure and a small amount of greenish fluid in which undigested food particles were found.

The heart was essentially normal, except for marked displacement to the right.

The left lung was decidedly underdeveloped. The lobes were quite small. The apical portion of the upper lobe was fully expanded and appeared normal but the lower

FIG. 7. Pyelogram showing the left renal pelvis and ureter, also the spinal scoliosis.

portion of the upper lobe was collapsed. Most of the lower lobe was also collapsed and completely devoid of air. The right lung showed partial atelectasis. There was no evidence of pneumonia in either lung.

The lower mediastinum was partly digested on the left, as a result of the action of gastric juice.

The esophagus and the right diaphragm were normal. The left diaphragm was deficient in its postero-lateral aspect, leaving a window large enough to admit a man's fist. The edges of the opening were perfectly smooth and slightly thicker than the adjacent normal diaphragm. The appearance was that of a congenital deficiency of the diaphragm.

The bulk of the stomach and part of the transverse colon were found in the left

thoracic cavity. A small amount of the pyloric end of the stomach was found below the diaphragm. The stomach contained about a quart of undigested foodstuff. On the lesser curvature of the stomach, about 3 cm. from the esophageal opening, was found a perforation which allowed the stomach contents to escape into the left pleural space. There was some question as to whether the perforation was ante mortem or post mortem, but the microscopic examination showed the perforation to have occurred before death. A portion of the transverse colon was found in the left thorax, otherwise the gastrointestinal tract was entirely normal. The liver and kidneys were negative. The spleen showed acute splenic tumor. Final diagnosis:

1. Diaphragmatic hernia
2. Gastric ulcer with perforation into the thorax
3. Rudimentary left lung
4. Atelectasis
5. Pneumo-hydro-thorax, left (gastric contents)

Comments

From the appearance of the diaphragmatic opening, this patient undoubtedly also had a congenital hernia of the diaphragm. The sudden onset of his symptoms was apparently due to the perforation of his ulcer. If he had been sent to the hospital immediately after the onset of his pain, and if proper roentgen-ray study could have been made promptly, it is possible that the condition could have been recognized. Whether a surgical intervention could have been successful can only be a matter for speculation. An approach through the lateral thoracic wall might have exposed the ulcer and permitted repair.

Discussion

The above cases are examples of how nature can adapt body function to extreme congenital deficiencies of structure and also what complications may develop to confuse the physician. They also demonstrate a few of the possible combinations of symptoms which may occur in diaphragmatic hernia. It is only necessary to reëmphasize the statements made by others that the diagnosis can usually be made by roentgen-ray examination, but the possibility of this condition must first be considered as in many cases the symptoms may simulate cardiac, pulmonary, gastric, gall-bladder or intestinal disease.

Summary

1. True hernia of the diaphragm is a rare condition as shown by the infrequency of its recognition in many clinics.

2. Two cases of congenital hernia of the diaphragm with unusual symptoms and complications have been reported.

3. Symptoms of diaphragmatic hernia may simulate cardiac, pulmonary, gastric, gall-bladder and intestinal disease and should be considered in the differential diagnosis of many diseases.

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SPONTANEOUS HEMORRHAGE INTO THE SUPRARENALS (SUPRARENAL APOPLEXY) *

By GEORGE E. LEONE, B.S., M.D., *Madison Barracks, N. Y.*

HEMORRHAGE into the suprarenals is a rare occurrence which usually results fatally and is difficult to recognize. The diagnosis is rarely made until after autopsy. Suprarenal hemorrhages have been more frequently observed in the newborn and in young children. The degree of hemorrhage varies from small petechial areas in the suprarenal glands to massive hemorrhages with extensive destruction of suprarenal tissue. These conditions have been described in the literature as acute hemorrhagic adrenalitis, Waterhouse-Friderichsen syndrome, spontaneous suprarenal hemorrhage and suprarenal apoplexy.

The cause and origin of the hemorrhage into the suprarenals are not definitely known. In considering the etiology, one must first differentiate between suprarenal hemorrhages in the newborn and those which occur in older children and adults. In the newborn, trauma and asphyxiation in prolonged labor are contributory factors, according to some observers. Prolonged and difficult deliveries may easily lead to circulatory stasis in the infantile abdominal organs. The mechanical effect of Schultze's resuscitation method for the newborn has been mentioned as a possible cause. There is some relationship between eclampsia in the mother and vascular lesions of the suprarenals in the newborn according to other authors.[1] In hereditary syphilis of the newborn the suprarenals have been found to contain more or less extensive hemorrhagic areas.[2]

In older children and adults suprarenal hemorrhages have been found in the course of acute infectious diseases, especially scarlet fever, diphtheria, meningococcus meningitis and pneumonia.[3, 4] Alcoholism, syphilis, and hemophilia have also been associated with some cases.

Up to the present time there are two predominating theories which attempt to explain the origin of hemorrhages into the suprarenals. One view lays stress upon the suprarenal vascular system; the other considers some lesion of the glandular parenchyma to be the primary cause. The evidence appears to be more convincing in support of some disturbance of the suprarenal circulatory system, which may be derived from a condition either of vascular traumatism, venous thrombosis, or bacterial emboli in the capillaries of the gland. In hitherto

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Report of case in an adult: From the Medical Service of the Sternberg General Hospital, U. S. Army, Manila, Philippines.

published cases of suprarenal apoplexy, venous thrombosis in the suprarenal glands has been definitely established.[1, 5] Whether this venous thrombosis, a sign of circulatory disturbances in the gland, is the cause of the hemorrhages, or whether the hemorrhage is due to a lesion of the suprarenal cells and the thrombosis represents only a result of the disturbances in the parenchymal congestion, is questionable. Few authors consider the primary injury to the organ as the essential cause of suprarenal hemorrhage in older children and adults.

Anatomically, the vessels of the suprarenal glands are characterized by extraordinary fineness of their walls and intimate contact with the cells. This may account for the greater frequency of suprarenal hemorrhages in the newborn as a result of venous congestion in the course of difficult, prolonged labor.

The clinical manifestations of hemorrhage into the suprarenal glands depend upon the degree of hemorrhage and the resultant destruction of suprarenal tissue. Since all the cases reported are those that have resulted in death, and have come to autopsy, most of our knowledge is confined to extensive hemorrhages of the suprarenals.

The signs and symptoms of spontaneous hemorrhage into the suprarenal, or suprarenal apoplexy, are those of sudden, total suprarenal insufficiency, characterized by circulatory collapse. Associated with this, there is usually a characteristic generalized purpuric eruption of the skin. The onset is sudden and alarming, and death ensues rapidly, usually within 24 hours. The patient appears to be in shock; the blood pressure is low and sometimes not obtainable; the pulse is small and rapid, respirations are increased, and the extremities are cold. There is marked pallor at the beginning of this condition, but later this is replaced by cyanosis which finally resembles postmortem lividity, especially over the back and hips. Severe gastrointestinal disturbances, with nausea, vomiting, and abdominal pains are present.[6, 7, 8] The temperature rises rapidly to a high level,[9] and drops immediately before death. The patient remains mentally clear. The picture is not unlike that seen in the splanchnic shock of acute hemorrhagic pancreatitis.[10]

The purpuric eruption of the skin found in most reported cases of suprarenal hemorrhage, especially in older children and adults, is most characteristic. It may resemble a purpura hemorrhagica, which in children is considered as the most probable diagnosis before blood studies are made. This purpuric eruption is reported with remarkable consistency in suprarenal hemorrhages that have ended in death. Even as early as 1904, Langmead,[11] in the Lancet, reported three cases of suprarenal hemorrhage in older children, each of whom had a purpuric or petechial eruption over the entire body. In two cases reported by Rabinowitz[12] in 1923, each child had this generalized eruption. Herrick observed this same eruption in the cases of massive adrenal hemorrhage associated with meningococcus meningitis in Army service during World War I. These purpuric spots appear shortly after the onset, and are first seen on the trunk and the extremities. The petechiae are bluish-red to purple in color, and increase in size. They may be found on the palms of the hands and the soles of the feet. About the smaller joints, and especially the hands, these petechial spots appear to coalesce. The entire body may be covered with this eruption; and it persists for several hours after death. There is no serum beneath the spots. Associated with the eruption there is usually a postmortem lividity of the skin, especially in the dependent regions.

The blood findings have not been uniform enough to support any conclusions, although there is a tendency to high leukocytosis.[13]

Treatment in these cases has been directed towards combating the sudden collapse of the circulation due to sudden adrenal insufficiency. The administration of 10 per cent dextrose in physiologic solution of sodium chloride intravenously is indicated. The addition of a few minims of a 1:1000 solution of adrenalin may be used. Certainly, if the diagnosis of adrenal insufficiency is made, the administration of extract of adrenal cortex is warranted.[14]

Herewith is reported a case of bilateral spontaneous hemorrhage into the suprarenals of an adult:

C. A. K., a 43 year old white male, unmarried, was admitted to Sternberg General Hospital, Manila, P. I., on December 26, 1937, at 5:00 p.m. complaining of gastrointestinal distress and weakness in the lower extremities.

Personal History. He had been a soldier for the past 11 years. Previous to that time he had worked on farms. He had served a tour of duty in the Philippines in 1929, had returned to the States, and at the time was serving a second tour in the Philippines. In 1927 he had contracted syphilis, for which he was under treatment for six years. He stated he had become seronegative. In 1929 he had been treated for bubo and also for "stomach trouble."

To his knowledge there were no familial diseases.

The patient was a steady drinker and frequently went on an alcoholic debauch. Such episodes lasted about two to three days, during which time he drank a quart of whiskey daily.

History of Present Illness. The patient was alert and oriented. He stated that he was getting over a mild drinking spree when, shortly before admission, he felt very weak and had pain in the abdomen associated with nausea. Shortly after admission he complained of pain, particularly in the epigastrium, and vomited several times; this vomitus was green. The temperature was 100° F. on admission. He continued to complain of abdominal distress, and in two hours the temperature went to 104.2° F. Later he complained of pain in the hips.

At 4:00 a.m., 11 hours after admission, the patient was seized with severe cramplike pain in the abdomen, and the examining physician at that time noticed purpuric eruptions on the abdomen and extremities. They were widely scattered. There was no spasm or rigidity of the abdominal muscles.

At 7:00 a.m. the patient suddenly became alarmingly worse. On inspection he seemed in shock. The pulse could not be felt at either wrist. The lips were blue. No blood pressure could be obtained on several attempts. The entire trunk and body, including the upper and lower extremities, were covered with a petechial eruption ranging from dark blue to black in color. Adrenalin was given; later digitalis preparations were used, and heat was applied to the entire body. The heart tones were distant; no murmurs were heard; the rhythm was regular. The lungs filled with moist crepitant râles throughout both sides; respirations were increased in rate but not labored. The abdomen was soft. The liver and spleen could not be palpated. The pupils were equal and reacted to light; there were coarse tremors of the hands. The patient was given 10 per cent dextrose in physiological solution of sodium chloride intravenously at once; he appeared to regain some color after this was given. The blood pressure now obtained was 76 mm. Hg systolic and 60 mm. diastolic. The heart tones were still weak.

The dependent portions of the body, particularly the back and buttocks, were assuming a postmortem lividity. The petechial eruption seemed more intense. The patient was rapidly sinking to the original state of collapse. He was mentally clear. The temperature dropped from 106° F. to subnormal shortly before 11:00 a.m. The

extremities were rapidly becoming cyanotic. At 11:00 a.m., while conversing with his physician the patient suddenly died.

Laboratory Findings	: Red blood cells 3,290,000.
	: White blood cells 37,850.
Differential	: 91% polymorphonuclears.
	: 6% lymphocytes.
	: 3% monocytes.
Platelets	: 200,000.
Coagulation time	: 3 minutes.
Bleeding time	: 2¼ minutes.
Icterus index	: 8
van den Bergh	: Delayed direct reaction.
Blood culture	: Negative.

Urine was positive for albumin, and coarse granular casts were found.

Diagnosis. 1. Circulatory collapse of unknown cause. 2. Purpura hemorrhagica, non-thrombocytopenic type.

Autopsy. The autopsy was performed three hours after the patient's death.

External examination: The body is that of a well developed and well nourished white American male. Postmortem rigidity is moderate. Lividity is marked, especially in dependent portions. Pupils are dilated and equal in size. Nares and external auditory canals are negative. A frothy fluid exudes from mouth. Right inguinal region shows an old healed linear scar. Entire surface of skin shows a purpuric type of rash or mottling. These areas are bluish-red, discrete, and vary in size from pinhead to one centimeter. They are present in the thick skin of the hands and feet.

Thorax: Both pleural cavities contain a small quantity of clear straw-colored fluid. No adhesions present.

Both lungs are voluminous and boggy throughout. A few superficial small red spots are present in the interlobar pleurae. On section, much frothy fluid escapes.

Heart: Pericardial sac and cavity normal. Right auricle and ventricle contracted and of moderate thickness. Cardiac muscles pale, red, and moderately firm. Coronary arteries patent.

Abdomen: Stomach dilated, small and large intestines are markedly contracted. No free fluid present. Appendix normal. Liver moderately enlarged. Surface smooth and pale yellow, mottled with brighter red intermingled tissue. On section, tissue appears as surface. Gall-bladder is thin walled, distended and filled with thin bile. Common duct patent. Spleen moderately increased in size, and soft. Kidneys normal size and dark red. Capsule easily removed. Surface capillaries distinct. On section, moderate congestion present. Pancreas normal in appearance.

Suprarenals: Left suprarenal is enlarged and enclosed in a large mass of fatty tissue. On section, medullary portion shows a hemorrhage which has practically destroyed it and infiltrated into the cortex. Right adrenal is small, dark red, and firm. On section, there is a diffuse hemorrhage throughout.

Gastrointestinal tract: Stomach is dilated and filled with greenish gray fluid material. Mucosa slightly congested. Intestines contracted and contain very little greenish mucoid material. A few areas of slight congestion present. No hemorrhages found in either stomach or intestines.

Bladder negative.

Scalp and skull normal. Brain: Slight congestion found.

Pathological Findings:

1. Hemorrhage, spontaneous, suprarenals, bilateral.
2. Edema of lungs.
3. Fatty infiltration of liver with acute congestion.
4. Congestion, acute, of kidneys.

Histological:

Suprarenal: The capsule shows a very slight degree of irregular thickening. The normal architecture of the tissue is obliterated greatly by the presence of massive hemorrhage. The zona glomerulosa is not distinct and clear cut. Only small collections of cells are robust and contain an abundant amount of lipoid substance. The zona reticularis is not distinct, because of the marked hemorrhage. However, the cellular pigment stands out prominently. Only a small amount of medulla is noted in the sections, and here the cellular picture is indistinct because of the marked hemorrhage. No tumor or inflammatory exudate noted. The large vessels present in the outer hemorrhagic fat tissue are thick walled, showing prominent intimal and medial thickening.

Spleen: Capsule thickened. Congestion is prominent. Occasional irregular areas of hemorrhage are noted. Cellular proliferation is prominent. Trabeculae are thick and prominent. The malpighian corpuscles are not remarkable. The central arterioles are thickened and show intimal hyalinization.

Liver: The parenchyma shows marked diffuse fatty metamorphosis. The central veins are dilated and engorged. There is prominent central capillary congestion. The portal vessels are dilated and engorged. There is no significant portal cellular reaction.

Pancreas: Not remarkable, except for slight fatty infiltration.

Kidney: Congestion is marked. The normal architecture of the glomeruli is obscured by the marked congestion. The tubular epithelium is not remarkable. There are no significant arteriosclerotic changes noted, nor is there any cellular inflammatory exudate present.

Brain: The meningeal vessels are dilated and engorged. No exudate noted. The parenchyma is not remarkable except for prominent capillary engorgement.

Histological Diagnosis:

Suprarenal : Hemorrhage, massive.
Spleen : Hyperplasia, acute toxic (acute splenic tumor).
: Congestion marked.
: Hemorrhage.
Liver : Fatty metamorphosis, severe. Congestion.
Brain : Congestion, meningeal, and parenchymal.

Summary and Conclusions

Spontaneous hemorrhage into the suprarenals is a rare condition, characterized by sudden onset of circulatory collapse associated with generalized purpuric eruption, and resulting in rapid death. Diagnosis is rarely made before death. The cause and origin of suprarenal hemorrhage are not definitely known. The condition must be differentiated from that occurring in newborn infants and that found in older children and adults. Venous congestion in prolonged difficult labors, hereditary syphilis, and eclampsia are the most frequent factors associated with suprarenal hemorrhage in the newborn. Acute infectious diseases, i.e., scarlet fever, diphtheria, meningitis, pneumonia, and disturbances of the circulatory system of the suprarenals are the more common conditions associated with suprarenal hemorrhage in older children and adults. Syphilis and alcoholism may play some part.

Thrombosis of the suprarenal vascular system, and injury to the parenchymal cells are the most frequent findings on histological examination. Acute suprarenal insufficiency results from the sudden disturbance of the glands, which, in turn, is in part the cause of the circulatory collapse. Circulatory collapse with

low or unobtainable blood pressure; rapid, small pulse; cold extremities and a generalized petechial eruption of the skin should make one suspicious of suprarenal insufficiency. Early recognition, with the administration of saline with 10 per cent glucose, and the use of extract of the suprarenal cortex seem to be the only hope in treatment of hemorrhage into the suprarenals at present.

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PERSIMMON PHYTOBEZOAR WITH CASE REPORT*

By JAMES H. MCNEILL, M.D., F.A.C.P., *North Wilkesboro, North Carolina*

PERSIMMON phytobezoar, nearly unknown in Europe, is ordinarily seen in the United States and Japan where the persimmon is native. Males, because they are more likely to eat persimmons under certain circumstances, are more frequently affected. Age seems to have no effect, cases having been reported between the ages of six and 75. Its presence is manifested within a relatively short time after ingestion of the fruit. There is, accordingly, a seasonal incidence, in the late fall and early winter, when the persimmons are ripening.

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Izumi, Isida and Iwamoto [1] defined the chemical and physical factors which combine to form the bezoar. They found that the element producing astringency in a persimmon is soluble shibuol, a phlobotannin composed of phloroglucin and gallic acid. This is present in large amounts in the unripe fruit and to a lesser degree under the fruit skin and calyx in the ripened fruit. This soluble shibuol is the cohesive material which aids in bezoar formation. The following paragraph is quoted from their report:

"One of the important properties of the soluble shibuol is that it is coagulated by the action of dilute mineral acids among others. We have proved also that the gastric juice, though weak in acidity, is capable of precipitating the soluble shibuol and coagulating it, with sufficient rapidity at body temperature. When the persimmon which still contains some soluble shibuol and accordingly is astringent in taste, is ingested unpeeled with skin, and especially when it is

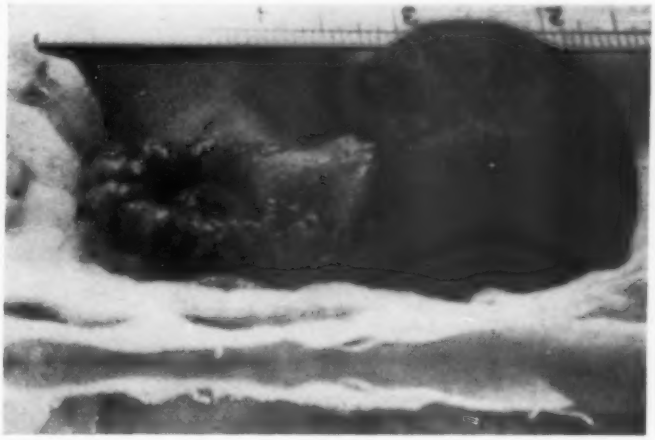

FIG. 1.

taken in alone or with only a little other food into an empty stomach, as it is in most of the reported cases, then coagulation of soluble shibuol will occur in the interfragmental spaces under the influence of the gastric juice. As the coagulum of shibuol is a sticky mass, it may cement the pieces of skin into a ball."

These workers succeeded in producing an artificial phytobezoar with persimmons only, although they tried many other fruits as well.

They formed these bezoars by incubating, at body temperature, gauze sacs of macerated fruits which had been slightly acidified with dilute hydrochloric acid. The concretion was found to be formed and to be rather firm in a relatively short time after incubation started. As they had found in two cases that the bezoars contained traces of pepsin and hydrochloric acid, but no bile constituents or trypsin, they concluded that these could have been formed only in the stomach. The soluble shibuol also has the faculty of coagulating proteins and starch, thus giving additional mass to the concretion. Furthermore the shibuol had the property of inhibiting the action of the digestive enzymes, thus preventing digestion of the mass before it could be solidified. We might expect putrefaction to cause some disintegration of the mass, but this also is inhibited by the shibuol.

Pathology. The bezoar itself has a dark brown or black shiny surface. On section it is a brown rather homogeneous mass having about the color of gingerbread (figure 1). The shape is variable, and the size between 5 and 7½ cm. in diameter.

The pathology most frequently resulting from the presence of the bezoar is a peptic ulcer, usually occurring in the prepyloric region. This ulcer may be attended by the usual complications, such as hemorrhage, perforation and peritonitis.

The indiscriminate use of purgatives may cause the passage of the bezoar, or a fragment thereof, into the duodenum causing mechanical obstruction.

Symptoms and Signs. From a review of 12 cases, including my own, it would appear that the presence of the phytobezoar produces few definite subjective or objective signs of specific diagnostic value (figure 2). Among these

Authors	Number of Cases	Symptoms + Signs															
		Nausea	Vomiting	Hematemesis	Severe Epigastric Pain	Dull Epigastric Ache	Abdominal Discomfort	Eructation	Sensation of Epigastric Lump	Peptic Ulcer Symptoms	Tarry Stools	Constipation	Diarrhea	Weight in Epigastrium	Intestinal Obstruction	Weight Loss	Tenderness	Palpable Mass
Izumi et al.[1]	2														2			
Copetti [2]	2		2			1								1				2
Allen [3]	3	1	2	1	1	1		1	2	2	1		1			3	1	3
Rutledge [4]	1									1							1	
Rodgers [5]	1	1	1		1		1					1				1		1
Ramstad [6]	1	1				1				1				1			1	
Wyatt [7]	1				1	1											1	1
McNeill	1					1	1	1		1						1		
Totals	12	3	5	1	3	5	2	2	2	5	1	1	1	2	2	5	4	7

FIG. 2

12 cases, the following symptoms and signs and their frequency were found as follows: Palpable mass in epigastrium, 7; weight loss, 5; dull aching sensation in the epigastrium, 5; peptic ulcer symptoms and signs, 5; vomiting, 5; epigastric tenderness, 4; nausea, 3; severe abdominal pain, 3. A sensation of a lump, eructation, intestinal obstruction, vague abdominal discomfort, and a sensation of a weight in the epigastrium were each complained of twice. Hematemesis, tarry stools, constipation, diarrhea, visible peristalsis were each mentioned once.

The times and modes of onset are variable. Acute symptoms may occur within a few hours after ingestion, but usually the onset is more insidious, probably with abdominal discomfort or a sensation of weight in the epigastrium. Still later, the symptoms of the complicating ulcer may dominate the picture.

Laboratory studies of the gastric contents give no information.

The diagnosis of bezoar depends upon the roentgen-ray study of the stomach with a barium meal. On fluoroscopy, a translucent mass is seen there. Usually,

this is situated in the pyloric end of the stomach, and it frequently may be dislodged and moved about by the examiner's hand. Ulceration of the stomach wall may also be detected. The roentgenograph also shows the translucent mass, and frequently an ulcer (figure 3).

Differential Diagnosis. Phytobezoar must be differentiated from gastric carcinoma, peptic ulcer, cholecystitis and the other upper abdominal diseases. The main differential points are the finding of the translucent mass on roentgen-ray examination of the stomach, and the history of the ingestion of persimmons.

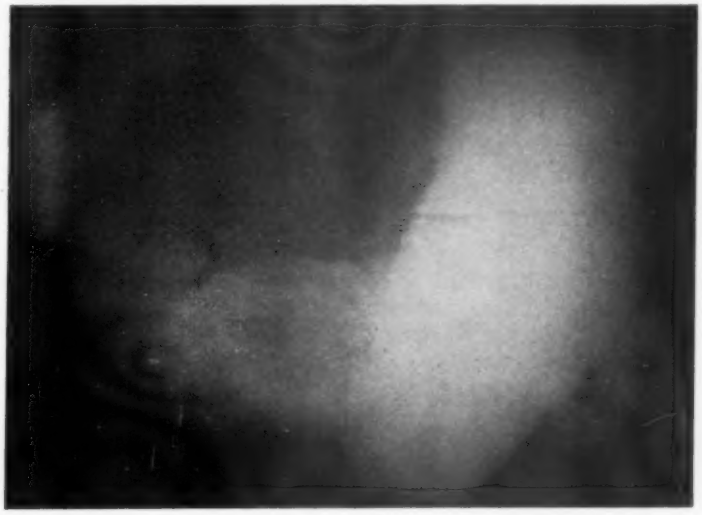

FIG. 3.

Treatment. Treatment, of course, is surgical removal. To expedite healing, an ulcer, if present, should probably also be excised.

No effort should be made to remove the bezoar by the use of purgatives, as such a procedure might cause the bezoar to pass into the intestine and cause obstruction.

CASE REPORT

A 57 year old white man came to me on April 4, 1939 complaining of stomach pain which had begun during the preceding fall. It was noted that this pain was more acute when his stomach was empty, and that eating gave relief from the pain. The taking of soda also gave relief. His sleep was frequently interrupted by epigastric pain which occurred irregularly between midnight and morning. There were no tarry stools. His only genitourinary complaint consisted of urgency and nocturia. He noted that the urinary stream was hard to start. He had lost about 10 pounds during the course of the present illness. His past history and habits gave no relevant facts. His father had died of paralysis, and his mother of "impaction of the bowels." Seven siblings were living and well. One brother had diabetes. One sister died of heart disease. One brother died of unknown cause, and one brother died of "creeping paralysis." The only positive physical findings were the presence of a bilateral pterygium, slight tenderness in the epigastric region, and a large prostate gland.

The story suggested peptic ulcer, but as the complaint appeared so late in life with absolutely no preceding stomach symptoms, it was realized that his symptoms might have been due to carcinoma of the stomach. He was referred to the hospital for roentgen-ray study. A roentgen-ray examination of the stomach made May 1 showed a large filling defect in the pre-pyloric region. In addition to this there was an oval shaped, translucent, movable mass in the stomach itself about two by three inches in diameter. A gastric analysis made at this time showed the gastric contents negative for occult blood. There were 31 degrees of free HCl, and 38 degrees total acidity. Twenty minutes after ingestion of a 7 per cent alcohol test meal, there were 76 degrees of free HCl and 80 degrees total acidity. Blood studies and urinalysis were completely normal.

From the above findings, a diagnosis of peptic ulcer was made. The movable, translucent mass in the stomach was considered to be a pedunculated epithelioma. An exploratory laparotomy was done on May 6, 1939. At operation, it was found that there was an ulcer on the greater curvature of the stomach about midway between the middle of the stomach and the pylorus. There was a large black hard foreign body found free in the lower end of the stomach. Operation consisted of removal of the foreign body with resection of the ulcer. The pathological report on the tissue removed was as follows: "This specimen shows a deep excavation with a rather sharp boundary. The floor of the ulcer consists of granulation tissue covered with a narrow zone of necrotic material, while deeper there is a considerable area of old scar tissue extending well into the muscle and at places extending to the epithelium. There is only a moderate amount of leukocytic infiltration in and beneath the ulcer and extending a short distance beneath the neighboring mucosa. There is no indication whatever of cancer. The brown mass accompanying the piece of stomach consists of necrotic material not identifiable."

From these findings the diagnosis was peptic ulcer probably due to phytobezoar. Inquiry after the operation revealed that the patient had eaten quite a large quantity of persimmons in the middle of an afternoon in the preceding fall just before the onset of the presenting symptoms. He had taken neither food nor water within several hours after the ingestion of the persimmons. The ulceration in his case evidently was due to the presence of the foreign body. Removal of the foreign body alone probably would have cured the ulcer, as that is the experience in most similar cases. However, he made an uneventful recovery, and has had no gastrointestinal complaints since operation.

Conclusions

1. Persimmon phytobezoars are formed in the stomach through the interaction of soluble shibuol and the gastric acids.
2. Such formations are aided by eating the whole persimmon, when the stomach is empty and no food or water is taken soon thereafter.
3. Phytobezoars may produce vague gastrointestinal symptoms and may cause ulceration of the gastric mucosa.
4. The diagnosis is made on the finding of a translucent mass in the stomach on roentgen-ray examination and upon the history of eating persimmons.
5. Treatment consists of surgical removal.
6. *Unpeeled persimmons should not be eaten when the stomach is empty.*

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ARTERIOLAR DISEASE OF THE HEART *

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Arteriolar disease of the heart is relatively rare. In a large autopsy service it is occasionally found with the more severe grades of coronary arteriosclerosis. Plaut and Kramer [1] have reported a case of hyaline degeneration with extensive myomalacia and relatively intact coronary arteries. This report deals with a case of severe cardiac failure and complete heart block, with widespread medial hypertrophy of the arterioles of the heart, minimal changes of the larger coronary arteries, a diffuse thickening of the parietal endocardium, intact valves and microscopic necroses of the myocardial fibers.

Case Report

The patient was a white man, 41 years old, of German descent, admitted to the City Hospital on July 9, 1935.

For 20 years he had suffered from cold hands, nose, ears and chin. Except for an attack of measles at the age of six, he had always been in good health. He was married and had one living child; his wife had had two miscarriages, both in the second month. In July 1922, he was examined for life insurance; no abnormalities were found; the pulse was 90, of good size, well sustained and regular. The blood pressure and urine were normal. In March 1923, a reëxamination was without significant findings. Venereal diseases were denied.

His present illness began in December 1933 with swelling of the feet, which would subside after short periods of rest in bed of two or three weeks. Weakness, dyspnea on the slightest exertion, and cough subsequently developed. He received treatment for cardiac dysfunction but the condition slowly progressed preventing him from carrying on his occupation of machinist. About January 20, 1935, the great toe of the left foot became swollen, red and tender. Soon the other four toes were affected and about a month later the great toe became ulcerated and discharged pus. On February 7, the great toe of the right foot became similarly involved and pain was constant. Two days later he was hospitalized.

Both feet were cold and cyanotic. All the toes of the left foot were gangrenous. Anterior tibial pulsation could not be felt. Both hands and the lower halves of the forearms were cold and cyanosed. The veins of the neck were dilated, and the pulsations, 110 per minute, were marked. The apex beat was visible and palpable in

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the fifth interspace 13.5 cm. to the left of the midline. The sounds were distant and of poor muscular quality and somewhat irregular. A loud blowing systolic murmur was heard over the apex and the base. The radial arteries felt thickened and sclerosed. The apical and radial pulses were equal in rate, 38 to 40 per minute. The blood pressure was, systolic 136, diastolic 98. The liver was palpable. The pupils were equal, regular, and reacted normally to light and in accommodation. The knee reflexes were normal. Fundus examination showed marked myopia; in the right eye patches of exudate, blurred disc margins and marked congestion were seen; in the left, the disc margins were raised, especially in the lower half, and a few patches of exudate were noted.

Roentgenography revealed an enlarged heart and pulmonary congestion. The blood Wassermann reaction was negative on two examinations. On admission, the non-protein nitrogen was 78 mg., and the uric acid 4.2 mg. per cent. In two weeks, the former had dropped to 36 mg. The urine was acid, its sp. gr. was 1.022; it contained 4 plus albumin, hyaline and finely granular casts, and red and white blood cells. The phenolphthalein excretion was 40 per cent in two hours. The Mosenthal test showed ability to concentrate to 1025.

On two occasions atropine was administered subcutaneously and he was observed over a six hour period. With a dose of 1/30 gr. the ventricular rate remained between 29 to 34, confirmed by electrocardiographic tracings. On the second occasion, one week later, the dose was increased to 1/15 gr. Within three hours he became delirious, the heart was unaffected, the rate remaining 31 to 35, and the respirations 26 to 30.

One week later 1 c.c. of 1–1000 adrenalin was given subcutaneously. Before administration the ventricular rate was 34, the blood pressure systolic 128 and diastolic 70. In fifteen minutes, the rate was 55, and the blood pressure 150/80. In five hours the rate fell to 34 and the blood pressure to 130/80.

He was discharged March 26, improved, with a diagnosis of obliterative endarteritis, heart block and chronic myocarditis.

On June 8 he returned to the hospital with the same complaints of cyanotic extremities and dyspnea on exertion. He remained for one month during which time his condition was not much changed. The heart findings were as before, the liver was palpable 8 cm. below the costal margin, the extremities were cyanotic, pulsation in the dorsalis pedis arteries was absent although there was no ankle edema. Both lungs had basal râles and there were signs of fluid in the right chest. Under digitalis he improved considerably. On discharge the liver was not palpable and he was free of dyspnea at rest.

On July 9 he was transferred to City Hospital where he remained until his death on October 5. The cervical venous pulsation was marked, with a ratio of three to one, the ventricular rate being 36. The pulses were full and the rate 36. The apex beat was in the sixth interspace, and the sounds were muffled. There was a distinct apical systolic and a questionable diastolic shock, but no thrills were felt. The blood pressure was 128 systolic and 64 diastolic. There was evident loss of weight, and the patient looked chronically ill. There was neither pain nor distress. The right pupil was irregular, and reacted normally to accommodation, sluggishly to light; the left was regular and reacted normally. An occasional moist râle was heard posteriorly at the right apex. The liver was palpable below the ensiform cartilage without pulsation or tenderness. There was no ascites. The extremities were slightly cyanosed. The Wassermann reaction was negative. The urea nitrogen measured 20 and 14 mg. per cent. The urine specific gravity was 1.024. It contained one plus albumin, a few waxy casts, and a very few white and red blood cells. The red blood cells numbered 5,400,000, and the white blood cells 9,500 with normal differential count. An electrocardiogram on July 10 showed complete heart block, an auricular rate of 90, and a ventricular rate of 34, QRS wide and notched, T_1 inverted.

He remained in surprisingly good condition and was able to take a moderate amount of exercise without any undue symptoms. Fundal examination revealed opacities of both corneae, principally in the central and lower halves, obscuring the right fundus; the left disc was somewhat pale with choroidal changes due to myopia.

On September 23 the extremities were cyanosed, the blood pressure 144/90, and some moisture was present in the lung bases. An electrocardiogram (figure 1) showed complete auriculo-ventricular block; auricular rate of 108; ventricular rate

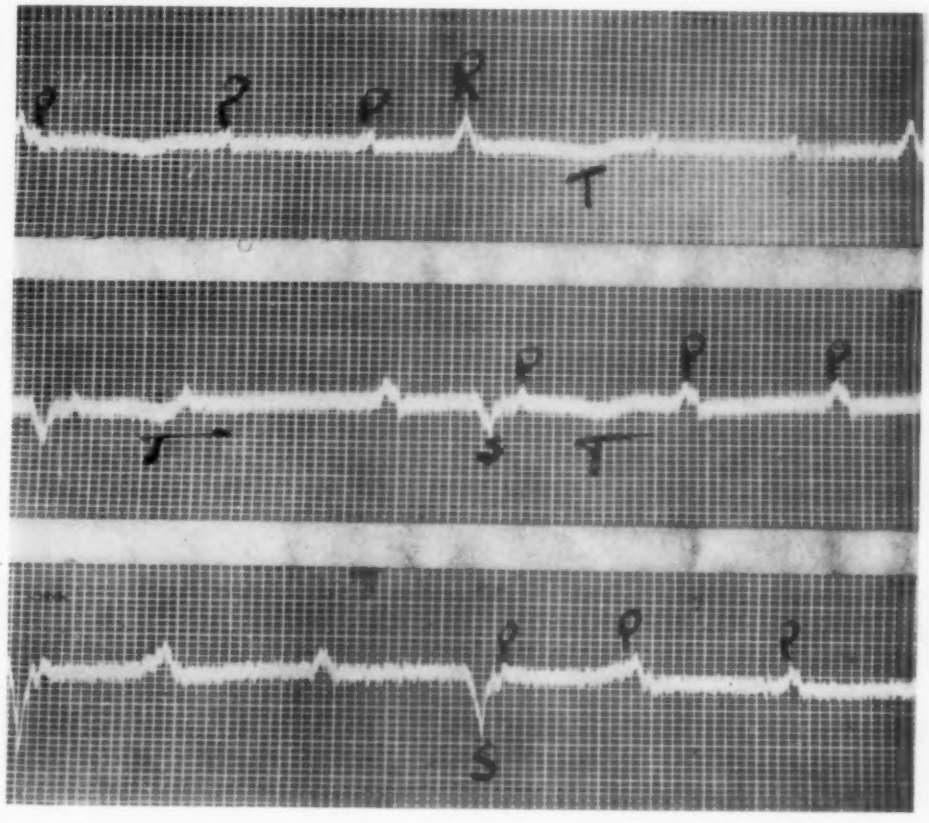

FIG. 1. Electrocardiogram taken September 23 showing complete heart block, intraventricular block and slight inversion of T_1 and T_2.

of 36; the QRS wide, notched, slurred, 0.12 sec.; the S–T interval, 0.44 sec.; the T-waves low voltage; and slight inversion of T_1 and T_2. Interpretation: complete heart block and intraventricular block.

He again improved but occasionally appeared mentally sluggish. On October 3, the right base was dull with diminished breath sounds and a few crackles. He was dyspneic, and the extremities were very cyanotic and cold. The pulse remained at 36. He was quite lethargic but clear periods were fairly common. On October 5, while talking, he became extremely cyanosed and died suddenly.

The temperature throughout remained between 97° and 99.6° F. and the pulse 32–40.

The final clinical diagnoses were coronary sclerosis, complete permanent heart block, chronic myocarditis and endarteritis obliterans.

A necropsy was performed 2½ hrs. after death. Only the pertinent observations are abstracted.

The body was that of a poorly nourished white man. The muscles of the left arm and leg were atrophic. There were 100 c.c. of clear fluid in the peritoneal and pleural sacs. Both lungs had fine stringy fibrous adhesions posteriorly and the right lung was bound down to the pericardium by dense thick adhesions. The lungs showed only a slight emphysema and slight chronic bronchitis. The liver, spleen and kidneys

FIG. 2. Heart, gross appearance of the mural endocardial fibrosis and intact valves.

were chronically engorged. The aorta contained a few atheromatous plaques. The other organs showed nothing of note. The peripheral arteries and the brain were not examined.

Heart: (figure 2) weight 425 gm. The pericardial sac was normal. The heart was only slightly dilated and of good consistence. The epicardial fat was scanty. The color as seen through the epicardium and on section was dark brown. The valves were normal. The endocardium of the right auricle had several areas of moderate thickening obscuring the underlying muscle. In the right ventricle was a thick fibrotic plaque involving the undefended space and the adjacent interventricular wall. On the posterior wall of the conus pulmonalis were several buttons of fibrosis joined together by linear thickenings of lesser involvement. The right ventricle

measured one cm. in thickness. The left auricle appeared normal. The left side of the interventricular wall showed an extensive diffuse white fibrosis of the endocardium extending from the base to the apex. The upper half measured 2 mm. in its thickest portion; in the lower half it was somewhat thinner and many abrupt thicker buttons were scattered over it. The process extended over the left ventricular endocardium but was more patchy in distribution and at the mitral sulcus, the involvement was minimal. Over the *columnae carneae* and papillary muscles the involvement was somewhat greater in degree. Small mural thrombi were present at the extreme apex.

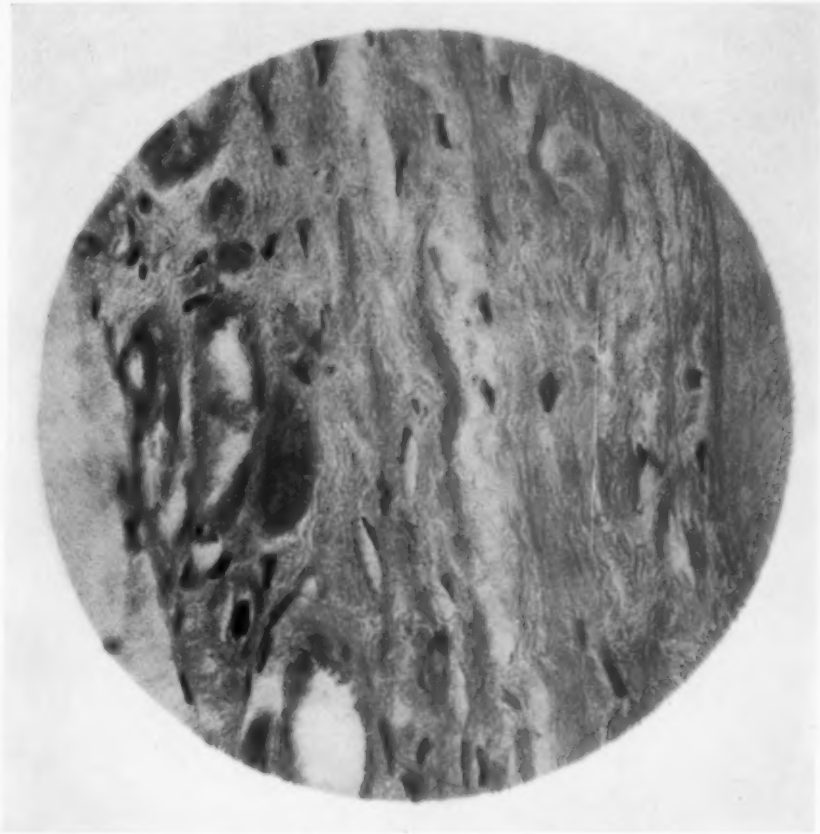

FIG. 3. Photomicrograph through the bifurcation of the bundle of His showing the marked fibrosis involving the branches with degeneration.

The myocardium showed a diffuse, fine, but rather inconspicuous fibrosis. The anterior descending coronary artery in its upper portion had one limited area of atheroma with narrowing of the lumen. The other arteries were remarkably free of change.

Microscopic examination: The endocardium was greatly thickened and fibrous, the fibrosis corresponding to the gross appearance, and involving the subendocardial areolar zone. In the thicker portions, elastic fibers were scanty or completely absent. In the regions of less marked involvement they were present in varying numbers and undergoing degenerative changes. Sometimes small inconspicuous foci of cellular reaction were seen in the deeper portions, usually in the regions of least involvement.

In the undefended space the endocardial fibrosis had involved the bifurcation of the bundle of His (figure 3) and the branches showed atrophy and degeneration. The main portion of the bundle was perfectly normal.

The hypertrophy of the myocardial fibers was much greater than the size or weight of the heart would indicate. It was generalized but more marked in the left ventricle and interventricular wall; in the right ventricle it was limited to the deep

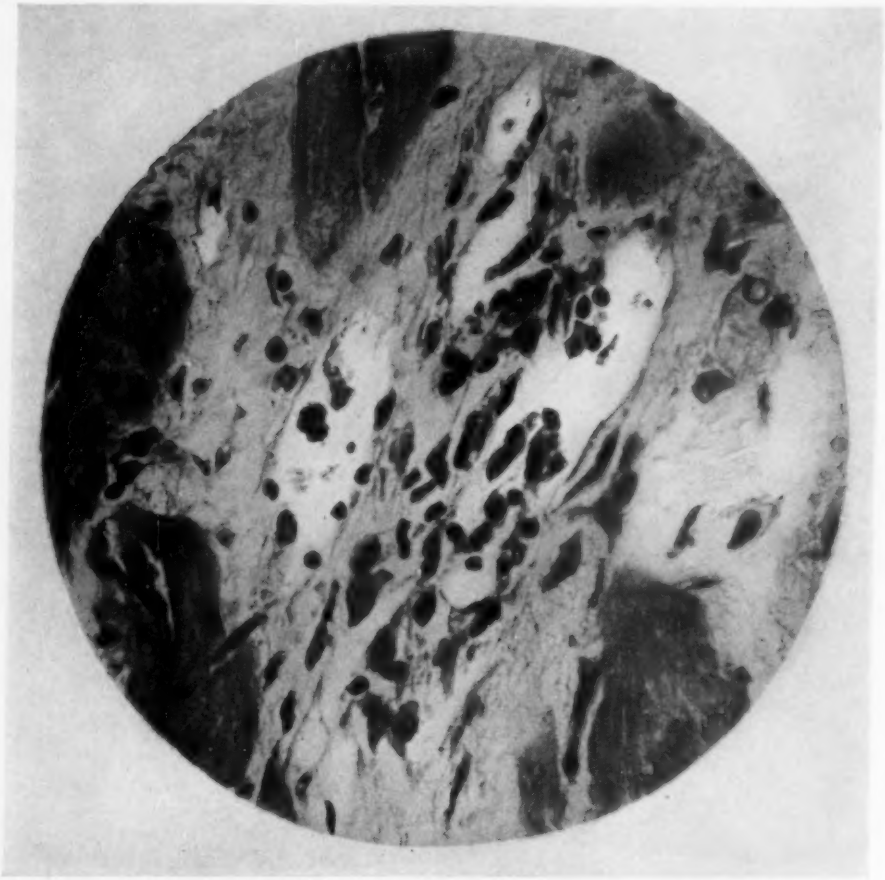

FIG. 4. Miliary necrosis of myocardial fiber with monocytic and lymphoid infiltration and granular degeneration of the cytoplasm.

muscle layer. There was a fine diffuse scarring of all ages, cellular to hyaline. In the left side a few large scars were present. Focal necroses (figures 4 and 5) involving only portions of the myocardial fibers were extremely numerous. The cytoplasm was replaced by a granular mass infiltrated by polymorphonuclear leukocytes, monocytes, and lymphoid cells in varying proportion. Frequently individual foci had a pure cell infiltrate. Early fibrosis was present in some of the older lesions.

The larger coronary arteries showed very slight atheromatous changes. In a small portion of the left anterior descending artery was a large plaque. The arterioles (figure 6) exhibited an intense medial hypertrophy. Degenerative changes were

absent. The arteriolar change varied considerably in distribution. It was most marked in the left ventricle and interventricular wall corresponding closely to the diffuse scarring and acute myocardial necroses. Even in these walls, it varied considerably in different regions.

The valves were normal.

The other organs show nothing remarkable.

FIG. 5. Miliary necrosis of a myocardial fiber of slightly earlier phase.

Anatomical Diagnosis: Arteriolar disease of heart; acute multiple miliary necroses of myocardium; fibrosis of myocardium; chronic parietal endocardial fibrosis; heart block; general chronic passive congestion.

DISCUSSION

Many interesting clinical and pathological features distinguish this case. The course showed a relentless progress of cardiac dysfunction of rather short duration, less than one year, complete heart block, and peripheral cyanosis of the extremities presenting some evidence of periodicity. The more common

causes of heart block [2] are coronary arteriosclerosis, syphilis, rheumatic heart disease; the rarer are trauma, congenital heart disease, bacterial endocarditis, miliary tuberculosis and neoplasm. Syphilis, rheumatic heart disease, trauma, bacterial endocarditis and miliary tuberculosis could quite readily be eliminated on clinical grounds. Heart block in congenital cardiac disease is usually associated with a defect of the interventricular septum, no signs of which were ever

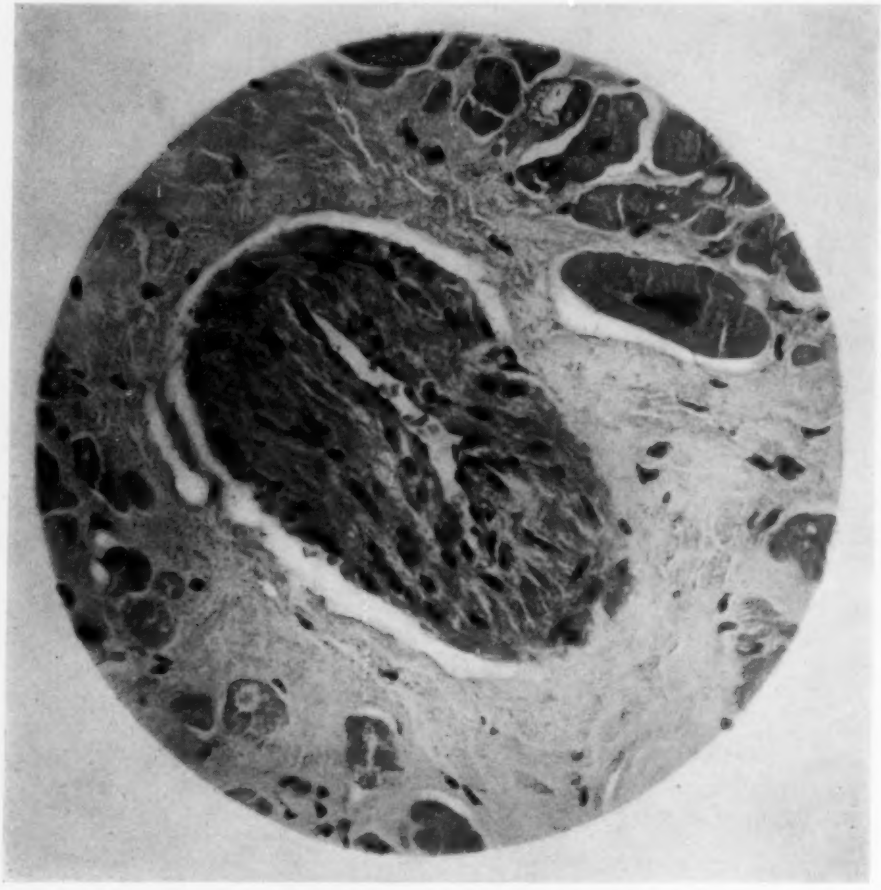

FIG. 6. Medial hypertrophy of arteriole of heart.

elicited in this case. Neoplasms occasionally cause it. They are most frequently metastatic and the original tumor has usually been productive of definite clinical symptoms while the cardiac signs are almost invariably terminal phenomena. Primary tumors of the heart causing block are much rarer; they usually are angiomas of the bundle and node and display clinically the Stokes-Adams syndrome. The peripheral symptoms displayed in the present case would also not be of help in an explanation of any of the usual causes of heart block. All these factors then could be eliminated as possible clinical diagnoses. Their elimination was confirmed by necropsy.

The most common cause of cardiac dysfunction is arteriosclerosis of the coronary arteries. At the age period of this patient, coronary arteriosclerosis is usually associated with a raised blood pressure due either to chronic glomerulonephritis or to essential hypertension. The absence of hypertension appeared to rule out both of these conditions. Arteriosclerosis of the coronary arteries on a non-hypertensive basis appeared remote. Such cases, as they come under our observation, are almost invariably in old individuals, the senile group, with marked evidence of the decrescent type of vascular disease. With any type of coronary arteriosclerosis, if peripheral lesions are present they seldom attack both arms and legs. On a clinical basis, therefore, although the diagnosis of coronary sclerosis could not be eliminated and seemed the most likely, it still left several questions unanswered. The necropsy demonstrated its absence.

Another diagnosis advanced was obliterative endarteritis. Pathologic data on the condition of the peripheral vessels are lacking so no definite opinion can be advanced. However, endarteritis usually attacks only the lower extremities. When it progresses to gangrene, such as was present early in this case, it seldom regresses to the degree found here. Nor is it commonly associated with cyanosis of the hands and forearms, a feature which was of some prominence. Its existence as an entity appears to rest on a somewhat insecure foundation.

There remains then another possibility to consider, that of Raynaud's disease. Here also the lack of pathologic data makes this only a tentative and not an absolute diagnosis. There are several points, however, which give this assumption some support. The patient, between the ages of 20 and 40, suffered from cold extremities. At the end of this period gangrene of the toes occurred and when he first came under hospital observation, coldness and cyanosis of both upper and lower extremities were striking. On each subsequent admission the same feature was present. Unfortunately the clinical examination of pulsation in the peripheral arteries was not noted between the periods of cyanosis, but from the available data the diagnosis of Raynaud's disease seems plausible.

Can Raynaud's disease be the factor underlying the unusual arteriolar disease of this heart? Hunt [8] does not mention it as a possibility.

The hypothesis of Raynaud is that the vasomotor center is unduly irritable and that efferent impulses from the center lead to paroxysmal contraction of arterioles. As revealed by microscopy, the arterioles presented a marked medial hypertrophy suggestive of some overactivity of the muscular wall. Peripheral vascular changes only have been described in Raynaud's disease, none of the cardiac arterioles. In essential hypertension, however, changes in the smaller arteries of the body of a somewhat similar character are found, viz. reduplication of the internal elastic lamella. Although medial hypertrophy of the coronary arterioles is unusual in essential hypertension, it has been observed in some instances in material at the laboratory of the City Hospital. It probably represents work hypertrophy. The paroxysmal contraction in Raynaud's disease could also result in medial hypertrophy, similarly a work hypertrophy from another cause. On this basis therefore it seems not unreasonable to look upon the cardiac vascular changes as having some relationship to Raynaud's disease.

There remains then the explanation of the myocardial and endocardial changes. If the case is one of vasoconstriction with an attendant hypertrophy affecting the cardiac arterioles, spasm leading to anoxemia could result in myocardiac necrosis followed by cellular reaction and fibrosis producing the his-

tological changes encountered. Involvement of the subendocardial zone of muscle, a condition also found in this heart, could likewise result in the parietal endocarditis. Endocardial fibrosis over an old infarct, which is simply necrosis on a massive scale, is a commonly recognized sequel. The cause of the heart block is evident, involvement of both branches at the bifurcation by scar.

There is still one other feature to be considered, the terminal episode of sudden death. The death appears certainly to have been cardiac and quite probably due to ventricular fibrillation. In a previous communication [4] it has been suggested by one of us (J. R. L.) that the summation of ectopic beats from multiple foci of hyperirritability due to recent myocardial damage may result in ventricular fibrillation. The conditions present in this case appear to fit this theory.

Summary and Conclusions

A case of arteriolar disease of the heart of unusual character is reported. The course was that of relentless progress of cardiac dysfunction, complete heart block and signs suggestive of Raynaud's disease. The necropsy showed medial hypertrophy of the arterioles of the heart, minimal changes of the larger coronary arteries, diffuse fibrosis of the parietal endocardium, intact valves and microscopic necroses of the myocardial fibers. The hypothesis is advanced that the arteriolar changes of the heart are directly related to Raynaud's disease and that these changes are causative factors in the myocardial degeneration and endocardial fibrosis. The heart block appears to have been due to involvement of the branches at the bifurcation of the bundle of His by the endocardial scarring.

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2. White, P. D.: Heart disease, 1935, Macmillan Co., New York, p. 673.
3. Hunt, J. H.: The Raynaud phenomena: a critical review, Quart. Jr. Med., 1936, xxix, 399.
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EDITORIAL

"HYPERINSULINISM" AND "SPONTANEOUS HYPOGLYCEMIA"

DURING recent years there have been two advances in our knowledge of hyperinsulinism. The first is the report of additional proved cases of this interesting condition; the second is the increasing insistence that the term hyperinsulinism be reserved for those cases in which there is proof that the symptoms are caused by the excessive production of endogenous insulin. In all other cases in which hypoglycemia is a finding the condition should be diagnosed as "spontaneous hypoglycemia."

True hyperinsulinism is a rare disease. Frantz,[1] who recently reviewed the world literature, found only 96 cases in which the diagnosis had been proved at operation or necropsy.

Hypoglycemia, on the other hand, is much more common and may be present either "physiologically" or owing to any one of many disturbances in carbohydrate metabolism. It may be related to a disorder in absorption or utilization of food as in certain diseases of the liver or due to a disturbance in those glands concerned directly or indirectly with carbohydrate metabolism. Hypoglycemia has been reported in connection with disturbances in the nervous system or the thyroid, adrenal, pituitary and sex glands. Not always, however, is the degree of hypoglycemia sufficiently severe to produce significant symptoms. Meakins [2] reported three cases of postencephalitic Parkinson's disease in which attacks of convulsions were associated with low concentrations of sugar in the blood. He urged further search for other cases in which a connection between a hypothalamic lesion and hypoglycemia was suggested. Adlersberg and Friedman,[3] who reported on disturbances of carbohydrate metabolism in 21 cases of postencephalitic Parkinson's disease, observed pathologically low levels of sugar in the blood in only three cases and these levels were observed after administration of 50 gm. of glucose. Hypoglycemia was reported by Rathery, Dérot and Sterne [4] in two cases of subdural hemorrhage and by Birnbaum and Wood [5] in cases of general paralysis.

Hypoglycemia may be present in many cases without organic disease. Matthews [6] determined the postabsorptive concentration of sugar in the blood of 117 normal persons and found that it ranged from 0.06 to 0.11 gm. per 100 c.c.; in 70 per cent the values fell between 0.07 and 0.08 gm. Hart

[1] FRANTZ, V. K.: Tumors of islet cells with hyperinsulinism; benign, malignant and questionable, Ann. Surg., 1940, cxii, 161.

[2] MEAKINS, J. C.: Hypoglycemia following encephalitis, Ann. Int. Med., 1940, cxiii, 1830.

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[4] RATHERY, F., DÉROT, M., and STERNE, J.: Hypoglycémie dans deux cas d'hémorrhagie méningée sous-arachnoidienne, Bull. et mém. Soc. méd. d. hóp. de Paris, 1931, xlvii, 1578.

[5] BIRNBAUM, LEO, and WOOD, J. A.: Hypoglycemia as a cause of seizures in general paralysis, Med. Bull. Vet. Admin., 1938, xiv, 236.

[6] MATTHEWS, M. W.: A study of the one dose three hour (standard) and the two dose one hour (Exton-Rose) glucose tolerance tests, Thesis, University of Minnesota, 1939.

and Lisa [7] analyzed all determinations of blood sugar made over a six year period at City Hospital, New York City. The data included routine determinations in 21,000 cases. In about 11 per cent the concentration of blood sugar was less than 0.08 gm. per 100 c.c.; in 7 per cent, between 0.070 and 0.079 gm.; in 2.3 per cent, between 0.060 and 0.069 gm.; in 0.8 per cent between 0.050 and 0.059 gm. and in 0.4 per cent less than 0.050 gm. Symptoms were absent in the entire group with the exception of one case in which the level of blood sugar was 0.030 gm.

Sufficiently strenuous exercise may produce severe hypoglycemia even among trained and healthy athletes.[8, 9] Patients who are nervous or high-strung seem less able than others to withstand effectively the strain placed on the homeostasis of the blood sugar by exercise. Michael performed several determinations of the concentration of sugar in the blood of each of 30 golfers in the course of 18 holes of golf after they had eaten their usual luncheon.[10] The values dropped to hypoglycemic levels (the average value was 0.054 gm. per 100 c.c.) between the ninth and fifteenth holes, or about two hours after the meal. The hypoglycemic period corresponded to a period of fatigue, mild symptoms of hypoglycemia and lessened efficiency, as reflected by poorer scores. Both the hypoglycemia and severity of symptoms were exaggerated among the poorer golfers, apparently because of tension, anxiety and greater output of energy, and were far less marked than average among the expert golfers, who were usually well poised and relaxed. A second observation was made on the same group after they had eaten food which contained more fat and less carbohydrate; consumption of sugar or candy at the seventh and eighth holes resulted in elimination of both hypoglycemia and its symptoms, and produced much better scores.

The term hyperinsulinism, then, should be reserved for those rare patients suffering from a serious disease, the result of the excessive secretion of insulin from a tumor of the islands of Langerhans; such patients should be subjected to surgical exploration. Thousands of other persons have varying degrees of hypoglycemia, with varying and usually vague complaints, caused by any one of many conditions. Hypoglycemia is not, in itself, a serious problem; such patients require, at most, more frequent feedings.

E. H. RYNEARSON

[7] HART, J. F., and LISA, J. R.: The rate of occurrence of hypoglycemia; a study of 21,000 routine fasting blood sugars, Endocrinology, 1940, xxvii, 19.

[8] LEVINE, S. A., GORDON, BURGESS and DERICK, C. L.: Some changes in the chemical constituents of the blood following a marathon race, Jr. Am. Med. Assoc., 1924, lxxxii, 1778.

[9] JOKL, ERNST: Sportärztliche Kasuistik, Klin. Wchnschr., 1933, xxii, 912.

[10] MICHAEL, PAUL: Blood sugar studies on golfers, Jr. Am. Med. Assoc., 1940, cxv, 286.

REVIEWS

The Heart in Pregnancy and the Childbearing Age. By BURTON E. HAMILTON, M.D., K. JEFFERSON THOMSON, M.D., and FREDERICK C. IRVING, M.D., F.A.C.S. 402 pages; 24 × 16 cm. Little, Brown and Co., Boston. 1941. Price, $5.00.

Many consulting internists have had the uneasy sensation that their knowledge concerning the behavior of the damaged heart in pregnancy was inadequate because of lack of sufficient experience with such cases during late pregnancy, labor and the puerperium. The problem of predetermining the risks of pregnancy to the cardiac is not one which should be assumed lightly. Even more difficult without specialized experience is the determination during pregnancy of the significance in the cardiac of certain changes in signs and symptoms. The decision as to the continuation of pregnancy and as to the relative risks of interrupting pregnancy and of carrying patients to term is a vital one.

The authors present the carefully studied experience of the Heart Clinic associated with the Boston Lying-In Hospital. It is the reviewer's belief that no more valuable addition to the working library of the practitioner, internist, cardiologist, or obstetrician has been made in recent years. The volume is divided into three books. Book I deals first with factual data as to incidence of cardiac disease among pregnant women, the classification of such cardiac cases, prognosis, etc. In Chapter 2 the causes of cardiac failure in pregnancy, the signs of failure, and the treatment of the cardiac are detailed. The methods of delivery (Dr. F. C. Irving) are discussed in the third chapter, and postpartum complications and after care are included in the fourth chapter.

Book II gives an extremely interesting account of what is known concerning the physiology of the circulation in normal pregnancy and in pregnant women with heart disease.

Book III takes up in eight chapters specific data concerning special types of heart disease in relation to the strain of pregnancy. The experiences of the authors and the literature of the subject are surveyed to round out the figures necessary for a statistical approach to the risks involved. Often available data are still insufficient. The chapter on congenital heart lesions includes data from the series of Dr. Maude Abbott.

The authors have made a contribution which will directly assist all physicians who have to deal with the pregnant cardiac. Moreover, it will stimulate others to consider more carefully the still unsolved problems in this field.

M. C. P.

Diseases of the Gallbladder and Bile Ducts. By WALTMAN WALTERS, B.S., M.D., M.S. in Surgery, Sc.D., F.A.C.S., and ALBERT M. SNELL, B.S., M.D., M.S. in Medicine, F.A.C.P. 645 pages; 24.5 × 16 cm. W. B. Saunders Co., Philadelphia. 1940. Price, $10.00.

The diseases of the gall-bladder and of the biliary tract are of particular interest to the internist. His experience with these conditions is large, and very frequently the results obtained are unsatisfactory. This volume presents the studies, the clinical methods and the results obtained in a Clinic which for half a century has had an exceptional group of physiologists, internists and surgeons who have devoted much time to the investigation and care of an extraordinarily large series of patients with biliary disease. The internist will profit by reading such a monograph and will find it useful for consultation on special topics. It is not an exhaustive treatise but it covers all important points adequately, and the references to the literature are sufficiently abundant for any necessary supplementary reading. It has the invaluable quality of

presenting problems from a practical working point of view which gives the reader some of the perspective of the authors as to the relative importance of certain facts and theories in this often confused field.

Part I is a relatively brief and very interesting review of the medical history and of the anatomy, physiology, pathogenesis and pathology of diseases of the gall-bladder and bile ducts. Part II is devoted to diseases of the gall-bladder; Part III to diseases of the bile ducts; Part IV to medical and surgical treatment; and Part V to preoperative and postoperative care. There is an appendix on technic. In addition to the chief authors who represent the surgical and medical interests in this field there are contributing authors who present special aspects.

The quality of the book is such that it should be in every hospital library. House officers and staff alike will find it valuable for consultation in relation to their daily problems in the diagnosis and treatment of diseases of the biliary tract.

M. C. P.

Diagnosis and Treatment of Menstrual Disorders and Sterility. By CHARLES MAZER, M.D., F.A.C.S., and S. LEON ISRAEL, M.D., F.A.C.S. 485 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. 1941. Price, $6.50.

The authors have furnished in this volume a very compact and complete discussion of their subject. This book should be invaluable to the general practitioner, specialist, and to one who wants a quick but accurate reference. The medical student should use this book only for reference as the scope is too wide for his limited knowledge.

The general disorders are discussed in a systematic manner, each in a separate unit which includes etiology, signs, symptoms and treatments. The treatments are discussed in detail, giving illustrations, case histories, technic and the exact doses of medication. The illustrations are very accurate and informative. A very important addition are the chapters on male sterility which are rather lengthy and well organized. This phase of the problem is often overlooked by many authors in discussing this subject, or they pass over it lightly.

The main difficulty with this discussion, as in many others of the day, is that so much of the treatment deals with endocrines which at the present time are in a constant state of flux. On the whole, the authors have covered the field thoroughly and have put into one volume the accepted and important knowledge of the subject.

The bibliography is excellent, and the appendix, containing dosages and potency of the various endocrine preparations, is a valuable adjunct.

E. I. C., JR.

Chemotherapy and Serum Therapy of Pneumonia. By FREDERICK T. LORD, M.D., ELLIOTT S. ROBINSON, M.D., and RODERICK HEFFRON, M.D. 174 pages; 21.5 × 14 cm. The Commonwealth Fund, New York. 1940. Price, $1.00.

This is the third in a series of handbooks on pneumonia therapy published by this Fund. The present edition includes chemotherapy as well as additional data on the use of horse and rabbit antiserum.

Diagnosis, typing and immunity factors are discussed somewhat briefly but in a quite adequate manner. The treatment with serum and chemotherapy is presented exceptionally well; exact methods of administration, precautions and dangers are clearly brought out.

The arrangement of the book is somewhat different from usual, inasmuch as the important headings are set forth in bold type in the margin of the page.

This book is highly recommended, and anyone treating pneumonia will find it an asset to his library.

W. K. W.

COLLEGE NEWS NOTES

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

Lt. Col. Daniel B. Faust, F.A.C.P., (MC), U. S. Army—"Diet Manual, Fitzsimons General Hospital";

Dr. David Warren Kramer, F.A.C.P., Philadelphia, Pa.—"Manual of Peripheral Vascular Disorders."

Reprints

Dr. Robert S. Berghoff, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Darrell C. Crain, Jr. (Associate), Washington, D. C.—1 reprint;
Dr. Norbert Enzer, F.A.C.P., Milwaukee, Wis.—3 reprints;
Dr. Irvin R. Fox (Associate), Eugene, Ore.—1 reprint;
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—1 reprint;
Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—1 reprint;
Dr. Saul Jarcho (Associate), New York, N. Y.—5 reprints;
Dr. Edward S. King, F.A.C.P., Wake Forest, N. C.—2 reprints;
Dr. Edward Kupka, F.A.C.P., Olive View, Calif.—2 reprints;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—2 reprints;
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—5 reprints;
Dr. J. Arthur Myers, F.A.C.P., Minneapolis, Minn.—15 reprints;
Dr. Louis B. Owens (Associate), Cincinnati, Ohio—1 reprint;
Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Lt. Col. James S. Simmons, F.A.C.P., (MC), U. S. Army—1 reprint;
Dr. Hugh Stalker, F.A.C.P., Detroit, Mich.—1 reprint;
Dr. Frederick Tice, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—1 reprint;
Dr. Oscar T. Wood, Jr. (Associate), Bywood, Pa.—2 reprints.

Regional Meeting of Florida Members of the College

On April 28 the Florida members of the American College of Physicians held their annual meeting in Jacksonville, Fla. The following program was presented:

Dr. James L. Borland, F.A.C.P., and Dr. Lucien Y. Dyrenforth, F.A.C.P., Jacksonville—"Erythrocyte Sedimentation Rate: A Comparative Analysis Based Upon Routine Clinical Data";

Dr. Karl B. Hanson (Associate), Jacksonville—"The Use of Cobra Venom and of Oxygen in the Control of Cardiac Pain";

Dr. J. Webster Merritt, F.A.C.P., Jacksonville—"Electrocardiographic T Wave Changes in Nonorganic Heart Disease."

Dr. Turner Z. Cason, F.A.C.P., Jacksonville, is the College Governor for Florida; Dr. Louie Limbaugh, F.A.C.P., Jacksonville, is President and Dr. Kenneth Phillips, F.A.C.P., Miami, is Secretary of the Florida Chapter.

The 13th Annual Spring Clinical Conference of the Dallas Southern Clinical Society was held at Dallas, March 17–20, under the presidency of Dr. Everett C. Fox, F.A.C.P., Dallas, Tex. Among the especially invited guests were the following:

Dr. Soma Weiss, F.A.C.P., Boston, Mass., four addresses—"Physiology and Interpretation of Common Symptoms in the Practice of Medicine," "New Drugs and New Uses of Old Drugs," "Etiology of Essential Hypertension," and "Pharmacologic Action and Clinical Use of Drugs Acting on the Autonomic Nervous System";

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Pa., three addresses—"Pitfalls in X-Ray Diagnosis," "Hodgkin's Disease," and "Roentgen Analysis of Fractures";

Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill., three addresses—"Sub-clinical States of Deficiency Diseases," "Diet in Medical Practice," and "Management of Obesity."

Dr. Nathan B. Van Etten, F.A.C.P., New York, N. Y., President of the American Medical Association, spoke on "American Health and National Defense" at a recent meeting of the Medical Society of the County of Kings and Academy of Medicine of Brooklyn.

The Board of Corporators of the Woman's Medical College of Pennsylvania recently appointed Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J., Acting President of the College, following the resignation of Dr. Chevalier Jackson.

Dr. Archibald A. Barron, F.A.C.P., Charlotte, was elected President, and Dr. Fonso Butler Watkins, F.A.C.P., Morganton, Vice-President of the North Carolina Neuropsychiatric Association at its recent meeting at Durham, N. C. Dr. Barron succeeds Dr. Mark A. Griffin, F.A.C.P., Asheville. Dr. Walter Freeman, F.A.C.P., Washington, D. C., gave the principal address at this meeting. He spoke on prefrontal lobotomies, a surgical operation on the brain which has produced beneficial results in certain cases of depression.

Dr. James L. McCartney, F.A.C.P., Philadelphia, Pa., Associate Director of the Medical Division of Sharp & Dohme, Inc., and Editor of the "Sharp & Dohme Seminar," has been appointed Medical Director of William R. Warner & Co., Inc., New York, N. Y., and affiliate organizations, effective April 1, 1941. Dr. McCartney graduated from Rush Medical College, University of Chicago, and has been associated with Sharp & Dohme since 1938. In his new position, Dr. McCartney will be chief medical advisor to William R. Warner & Co., Inc., and in charge of clinical research, in coöperation with the Warner Institute for Therapeutic Research, which is under the direction of Dr. M. R. Thompson.

Recently the British Medical Association gave a private luncheon in honor of Dr. Thomas Parran, F.A.C.P., Surgeon General, U. S. Public Health Service, Dr. John E. Gordon, F.A.C.P., Boston, Mass., who is acting as U. S. Liaison Officer with the Ministry of Health, and Dr. John R. Mote, who is now acting as Medical Advisor to the American Red Cross Committee in London. Sir Wilson Jameson, Chief Medical Officer to the Ministry of Health, was the other guest, and among those present were the principal officers and officials of the Association.

On March 17 Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, Pa., spoke on "The Reticulo-Endothelial System in Clinical Medicine" at a meeting of the Medical Officers of the War Department of the U. S. Army, Washington, D. C.

Dr. John M. Dyson, F.A.C.P., Hazleton, Pa., addressed a recent meeting of the Columbia County Medical Society at Berwick, Pa., on "Modern Treatment of Pneumonia."

Dr. Arthur J. Logie, F.A.C.P., Jacksonville, Fla., was the guest speaker at a meeting of the Leon County Medical Society at Tallahassee, Fla., on March 18, 1941. Dr. Logie spoke on "More Recent Advances in the Diagnosis of Tuberculosis."

Dr. Thomas J. Longo, F.A.C.P., Brooklyn, N. Y., has been elected Director of Medicine at the Coney Island Hospital, Brooklyn.

Dr. Albert E. Russell, F.A.C.P., New York, N. Y., has been promoted to the grade of Senior Surgeon in the U. S. Public Health Service. Dr. Russell has recently been assigned to the Army Second Corps Area at Governors Island, N. Y.

Among the speakers at the 31st meeting of the Brooklyn Society of Internal Medicine, held at the Methodist Hospital, Brooklyn, N. Y., were:

Dr. Henry D. Fearon, F.A.C.P., Brooklyn, N. Y.—"Remarks on Sulfathiazole";

Dr. Harold R. Merwarth, F.A.C.P., Brooklyn, N. Y.—"The Occurrence of Peripheral Facial Paralysis in Hypertensive Vascular Disease."

On April 16, 1941, Dr. Ralph Pemberton, F.A.C.P., Paoli, Pa., addressed the Medical Society of the District of Columbia, Washington. On April 30, 1941, Dr. Pemberton addressed the Long Island College Hospital Staff, Brooklyn, N. Y.

The American Academy of Physical Medicine held its 19th annual meeting and scientific session in New York, N. Y., April 28–30, 1941. Among the speakers at this meeting were:

Dr. Walter M. Solomon (Associate), Cleveland, Ohio—"Treatment of Epidermophytosis by Iontophoresis";

Dr. Irving Sherwood Wright, F.A.C.P., New York, N. Y.—"Physical Measures in Peripheral Vascular Disease";

Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—"Disabilities Encountered Among Veterans";

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn.—"Methods of Applying Heat Locally in General Practice."

Dr. Anthony C. Cipollaro, F.A.C.P., New York, N. Y., conducted a panel discussion on "Physical Medicine in Dermatology."

Among those who participated in a series of Friday afternoon lectures of the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn were:

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y.—"The Treatment of Infectious Arthritis," March 14, 1941;

Dr. Priscilla White, F.A.C.P., Boston, Mass.—"The Diabetic Child," March 28, 1941;

Dr. Frank Bethel Cross, F.A.C.P., Brooklyn, N. Y.—"Hypertension: Its Renal and Psychogenic Aspects," April 4, 1941.

The following members of the College presided at the round-table therapeutic reviews of this society:

Dr. Edwin P. Maynard, Jr., F.A.C.P., Brooklyn, N. Y.—"Treatment of Angina Pectoris and Coronary Thrombosis";

Dr. John H. Crawford, F.A.C.P., Brooklyn, N. Y.—"Treatment of Congestive Heart Failure";

Dr. Charles Solomon, F.A.C.P., Brooklyn, N. Y.—"The Use and Abuse of Hypnotics and Sedatives."

Dr. Maurice J. Dattelbaum, F.A.C.P., is President; Dr. Benjamin M. Bernstein (Associate), Associate Secretary; Dr. Abraham Klein, F.A.C.P., Associate Treasurer; and Dr. Edwin P. Maynard, Jr., F.A.C.P., Associate Directing Librarian and Curator of this society.

The following members of the College addressed recent meetings of the Medical Society of the District of Columbia, Washington:

Dr. E. Gurney Clark (Associate), Baltimore, Md.—"Clinical Epidemiology in the Management of Syphilis," April 2, 1941;

Dr. Charles R. L. Halley (Associate), Washington, D. C.—"The Clinical Diagnosis of Syphilis," April 2, 1941;

Dr. Worth B. Daniels (Associate), Washington, D. C.—"An Outbreak of Bronchopneumonia in a Girls' School," April 16, 1941;

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn.—"Differential Diagnosis of Psychoneuroses," April 21, 1941.

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., who has been Acting Dean of Yale University School of Medicine since the retirement of Dr. Stanhope Bayne-Jones in 1940, was appointed Dean, effective July 1, 1941. Dr. Blake joined the medical faculty of Yale as John Slade Ely Professor of Medicine in 1921 and served with that title until 1927, when he became Sterling Professor of Medicine.

Dr. George R. Minot, F.A.C.P., Boston, Mass., recently addressed the Essex County Medical Society at Newark, N. J., on "Etiology, Diagnosis and Treatment of the Anemias."

The annual Alumni Postgraduate Session and the Ernst A. Sommer Memorial Lectures of the University of Oregon Medical School, Portland, Ore., were given March 17–21, 1941. Dr. William S. Middleton, F.A.C.P., Madison, Wis., lectured on "Further Rationalized Therapeutic Experiences" and "Infectious Arteritis." During this Session Dr. Middleton led a luncheon round-table discussion on "Cardiac Emergencies."

Among the speakers at a recent meeting of the New York and Philadelphia Chapters of the National Gastroenterological Association, held in Philadelphia, Pa., were:

Dr. Anthony Bassler, F.A.C.P., New York, N. Y.—"Recent Advances in Gastroenterology";

Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—"Recent Advances of Hepatic Function Tests";

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Pa.—"Therapeutic Use of Cholesterol Ester Sol in Infectious and Toxemic Diseases."

The 9th annual Postgraduate Clinic of the George Washington University School of Medicine was held recently in Washington, D. C. Dr. Tom D. Spies, F.A.C.P.,

Cincinnati, Ohio, spoke on "Clinical Aspects of Nutritional Diseases," and Dr. Paul D. White, F.A.C.P., Boston, Mass., conducted a clinic on heart diseases at this meeting.

The 26th annual meeting of the Iowa Tuberculosis Association was held in Des Moines, Iowa, March 27–28. Among the speakers at this meeting were:

Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill.—"Trends During the Past Decade in the Management of Tuberculosis";

Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—"A Challenge to Iowa Colleges."

The annual Russell D. Carman Lecture was presented under the auspices of the St. Louis (Mo.) Medical Society on March 25, 1941. Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., gave the Lecture. His subject was "Cancer of the Gastrointestinal Tract: Its Early Manifestations."

Dr. Howard F. Root, F.A.C.P., Brookline, Mass., was one of the guest speakers at a meeting of the Philadelphia County Medical Society on March 12, 1941. Dr. Root spoke on "The Possibilities of Cure of Diabetes."

The National Tuberculosis Association, 1790 Broadway, New York, N. Y., will furnish, free to physicians, a copy of "Chest X-Ray Interpretation," by Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., upon request. This publication is made available in connection with the National Tuberculosis Association's 1941 campaign.

OBITUARIES

DR. HARRY BEECHER McCORKLE

On December 25, 1940, Dr. Harry Beecher McCorkle died in California of bronchopneumonia following influenza.

Dr. McCorkle was born in Coffeyville, Kansas, August 1, 1870. He attended the State University at Lawrence, Kansas, and was graduated in 1898 in Medicine from the St. Louis University School of Medicine then known as Marion-Sims College of Medicine.

He had a large practice in Colorado Springs for over 30 years. He had been a member of the general staff of the Glockner Hospital, Beth-El Hospital and Beth-El Sanatorium for many years. He was medical director of the National Methodist-Episcopal Sanatorium for Tuberculosis and specialist on tuberculosis for the Missouri-Pacific Hospital Association and Brotherhood of Railway Trainmen. He was a member of the El Paso County Medical Society, the Colorado State Medical Society, the American Medical Association, and the American College of Physicians. He was a member of the Masonic Lodge and the Knights of Pythias.

During his early life, he met and knew many of the interesting personalities famous in the early history of the Southwest. It is stated that he was in Coffeyville, Kansas, on the day the Dalton boys held up the town.

After receiving his medical degree, he returned to Oklahoma and prac-

ticed medicine at Billings for about ten years, during most of which time he was mayor of that city.

About the year 1910 he developed pulmonary tuberculosis and came to Colorado Springs where he was a patient in the Modern Woodmen Sanatorium for many months. After recovery he started practice in Colorado Springs and was very active in his profession until December, 1939, when he was forced to retire because of poor health.

Soon after his graduation from medical college, he married Miss Edna V. Becker. Mrs. McCorkle and three children survive; the children are Mrs. Cora McCluskey of Santa Rosa, California; Mrs. Helen Warner, Wickenburg, Arizona, and Jack McCorkle of Los Angeles, California. He is also survived by one brother and one sister who live in Oregon and Kansas, respectively.

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado

DR. DANIEL E. S. COLEMAN

Dr. Daniel E. S. Coleman, F. A. C. P., New York City, died February 27, 1941, at the age of sixty-eight.

Dr. Coleman was born in New York City, July 20, 1872, attended the University Grammar School, St. Louis College, and De La Salle Institute. He received the degree of Ph.B. from St. Francis Xavier College in 1894, and his M.D. degree from the New York Homeopathic Medical College and Flower Hospital in 1901. After an interneship at the Metropolitan Hospital, he held the following appointments: Anesthetist, 1903–04, Ophthalmic Hospital; Visiting Physician, 1904–09, St. Gregory Hospital; Consulting Physician, 1909–13, same; Assistant Visiting Physician, 1906–15, Metropolitan Hospital; Visiting Physician, 1915–28, same; Assistant Visiting Physician, 1904–13, Flower Hospital; Visiting Physician 1913–19, same; Instructor, Lecturer and Professor of Materia Medica, 1904–19, New York Homeopathic Medical College. In more recent years he was Senior Attending Physician and Secretary of the Board of Directors of the Community Hospital (Welfare Island).

For many years Dr. Coleman was a commissioned Major in the Medical Corps of the National Guard. He made many contributions to medical literature, some of them appearing as late as 1939. He was a former President of the American Association of Clinical Research, twice President of the Alumni Association of New York Homeopathic Medical College and Flower Hospital, a former President of the International Hahnemannian Society; member, Association of Military Surgeons of the U. S. A., American Institute of Homeopathy, Academy of Pathological Science. He had been a Fellow of the American College of Physicians since 1920.